Community acquired bacterial meningitis and meningococcal septicaemia amongst adults in England and Wales : epidemiology and clinical management

Thesis

Community acquired bacterial meningitis and meningococcal septicaemia amongst adults in England and Wales: epidemiology and clinical management

by

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Abstract

Background: Bacterial meningitis and meningococcal septicaemia are important causes of morbidity and mortality in the UK and elsewhere. There have been achievements in paediatric care, including vaccination; however mortality amongst otherwise healthy young adults remains high.

Objective: I undertook this study to examine the way by which the public health burden of meningitis in adults can be reduced.

Methods: I used routine surveillance data (laboratory reports, clinical notifications, hospital activity, mortality data) to examine the epidemiology and determine the changing trends. I undertook a capture-recapture study to quantify the underreporting through the routine surveillance. I conducted a retrospective review of clinical management of adult patients with meningitis in England and Wales using medical records of patients diagnosed with meningitis or meningococcal septicaemia. I examined the association of clinical management with the outcome of the disease (CABM and MS).

Findings: The epidemiology of adult meningitis in England and Wales is changing. Overall forms of CABM show no significant changing trend, whilst meningococcal septicaemia shows an increasing trend. Tubercular meningitis is increasing significantly, whilst pneumococcal, HiB and *Listeria meningitis* are falling. Mortality generally remains in a steady trend. There are differences by age-group and causative organisms. There is considerable (~50%) underreporting of both, incidence and mortality from all major routine surveillance systems. Hospital management of meningitis is largely sub-optimal. Main areas of deficiency in clinical care are: timely diagnosis and consequently administration of antibiotics, assessment of severity, and record keeping; and these appeared to vary between the hospitals. It is difficult to examine the association between clinical with the outcome of meningitis primarily

due to confounding by severity of illness which in my study was further jeopardised by the lack of recorded data and study power.

Conclusion: This study has identified areas within public health interventions, such as vaccination policies, and clinical care, such as improved diagnosis and severity assessment, where there is potential for improvement towards a reduced public health burden of adult meningitis in England and Wales.

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Abbreviations

ACHA - American College Health Association

BCG - Bacillus Calmette-Guerin

BIS - British Infection Society

CABM - Community Acquired Bacterial Meningitis

CCDC - Consultant in Communicable Disease Control

CDC, US - Centers for Disease Control

CDR - Communicable Disease Report

CDSC - Communicable Disease Surveillance Centre

CFI – Centre for Infection

CFR – Case Fatality Rate

CSF – Cerebro Spinal Fluid

CT - Computerised Tomography

DH - Department of Health

ECDC – European Centre for Disease Control and Surveillance

EP – Expert Panel

FSML - Food Safety Microbiology Laboratory

GAVI - Global Alliance for Vaccines and Immunization

HES – Hospital Episode Statistics

Hib - Haemophilus influenzae type b

HIV – Human Immunodeficiency Virus

HPA - Health Protection Agency

ICD 10 - International Classification of Diseases 10

ICP - Intracranial Pressure

IPD - Invasive Pneumococcal Disease

LEP - Laboratory of Enteric Pathogens

LP – Lumbar Puncture

MD - Meningococcal Disease

Men C – Menigitis Serogroup C

Men RU - Meningococcal Reference Unit

MREC - Multi-Centre Research Ethics Committee,

MS – Meningococcol Septicaemia

NHS – National Health Service

NM – *Neisseria Meningitidis*

NNT – Number Needed to Treat

NOID - Notifications of Infectious Diseases

ONS - Office for National Statistics

PCR – Polymerase Chain Reaction

PCV – Pneumococcal Conjugate Vaccine

PHLS – Public Health Laboratory Service

PI - Principal Investigator

PTC – Primary Care Trusts

RLR - Reconciled Laboratory Reports

RSIL - Respiratory and Systemic Infection Laboratory

SE – Standing Error

TB - Tubercolosis

TBM – tubercolous meningitis

US – United States

VPD – Vaccine Preventable Diseases

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Preface

In 1967 the United States' Surgeon General, Dr William Stewart declared that "with the advent of antibiotics and the broad use of vaccines, the war against infectious diseases had been essentially won".

Forty years on, however, the Director of the European Centre for Disease Prevention and Control, using less aggressive vocabulary, emphasised that it is "*a never-ending dance in which the human race needs to constantly find new technologies and tools to keep in step with changing and new microbes!*"[1]

As the research for this thesis has shown – if we fall out of the meningitis dance-step, the consequences are serious and in almost half of cases even tragic.

[1] Jakab, Z. (2007). "Why a burden of disease study?" Euro Surveill 12(12): E1-2.

***A case from the hospital review**: A young man, in his mid 30s, is admitted to hospital late at night presenting with "headache, confusion, and generally unwell". He is treated for symptoms of alcohol absenteeism. He doesn't improve, his conscious level deteriorates and in less then 48 hours later he is deceased. The results of the blood culture, a day after his death, show growth of Neisseria Meningitidis.*

This tragic case presents the three main messages of my research from this thesis:

1) Meningitis and septicaemia amongst adults occurs and is grave;

2) It is often undetectable;

3) The prevention and clinical management can and should do more to reduce the burden and improve the outcomes of this, yet another infectious death-causing disease.

Chapter One

Introduction to the thesis

Chapter One - Table of content

1.1 Introduction

This thesis presents an examination of the epidemiology and the clinical management of bacterial meningitis and meningococcal septicaemia. It focuses on the community acquired forms of meningitis, amongst adults aged 16 and above in England and Wales between 1990 and 2002.

The term Community Acquired Bacterial Meningitis (CABM) and Meningococcal Septicaemia (MS) will be used to define and include the relevant forms of meningitis included in this research.

1.2 The public health relevance

Bacterial meningitis and meningococcal septicaemia are important causes of preventable morbidity and mortality in the UK (Abbott, Jones et al. 1985; Stanek and Mufson 1999; Short and Tunkel 2000; Williams and Nadel 2001; Cartwright 2002).

All forms of bacterial meningitis examined in this thesis are notifiable diseases under the Public Health (Infectious Disease) Regulations 1988. Since 1998, an enhanced surveillance system records individual patient factors and links them to microbiological information from the national reference laboratories.

Understanding the epidemiology of bacterial meningitis and meningococcal septicaemia is essential to appropriate vaccine implementation and clinical management.

Amongst children, these conditions are important infectious causes of death and disability worldwide. Over the last decade, new protein-conjugate vaccines against *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC) have had a dramatic effect on the epidemiology of childhood meningitis in several industrialised countries, including the United Kingdom (Ramsay, McVernon et al. 2003)(Ramsay, Andrews et al. 2003). More recently, improvements in clinical

approach to meningococcal sepsis in particular, have been associated with a reduced mortality (Booy, Habibi et al. 2001).

Amongst adults, changes in the epidemiology of acute bacterial meningitis and meningococcal septicaemia, over this time period, are less well documented. In particular, it is uncertain whether an increasingly ageing population, a paediatric population with reduced carriage of common causative pathogens after vaccination and the resurgence of infections such as tuberculosis, have modified the spectrum of disease (MacLehose, McKee et al. 2002). Also, as the incidence of bacterial meningitis in children declines the relative public health importance of bacterial meningitis in adults increases.

The clinical management of meningitis and meningococcal septicaemia is challenging and is associated with high morbidity and mortality. There have been significant improvements in clinical management of paediatric meningitis, however in adults case-fatality remains high. The spectrum of the disease in adults differs from children and there are few comprehensive studies to determine the epidemiology of bacterial meningitis in this age-group. The demographics of the population of England and Wales is changing with an increasing proportion of older people. The number of immunocompromised people is also rising mostly due more chronic disease in the elderly and HIV infections. Therefore, information on the epidemiology of adult meningitis in this context will have important implications for public health as well as clinical management.

As will be presented in greater detail in the next chapter (2) Background, understanding the epidemiology and early recognition, stabilisation, assessment of severity and institution of specific therapy are crucial to patient outcome (NOTE: references to this chapter are merged into the refernces in Chapter 2, pg 81 - 101. Most adults with bacterial meningitis or meningococcal septicaemia present to clinicians with little experience of these conditions. To address this issue, in 1999 the

British Infection Society (BIS) published consensus guidelines for the management of acute bacterial meningitis in immunocompetent adults. However, these were not widely disseminated and there remains a perception amongst infection specialists that management of these conditions continues to be imperfect (Ninis, Phillips et al. 2005).

Therefore I set out this research, which is a national review of the epidemiology and the clinical management of community acquired bacterial meningitis and meningococcal septicaemia amongst adults in England and Wales.

1.3 Aim and objectives

To identify the potential areas for intervention to improve the prevention and clinical management and provide appropriate recommendations to decrease the morbidity and mortality from CABM in adults in England and Wales.

The objectives of this research were:

Objective 1. To examine the current epidemiology of CABM and MS among adults in England and Wales.

Objective 2. To improve current estimates of the incidence and mortality associated with acute bacterial meningitis and meningococcal septicaemia in adults.

Objective 3. To review the clinical management, including diagnosis and treatment, of adults presenting to randomly selected acute healthcare trusts, focusing on BIS standards.

Objective 4. To identify key areas of deficiency in current management of bacterial meningitis and meningococcal septicaemia in adults and make recommendations to improve management.

Objective 5. To examine any association between clinical management and the outcome of CABM and MS.

Objective 6. To generate appropriate recommendations for the public health and clinical management of bacterial meningitis and meningococcal septicaemia in England and Wales.

1.4 Layout and structure of the thesis

The thesis comprises: analysis of the changing epidemiology, application of statistical methods for improving the estimates from routinely available data, a review of the clinical management of these conditions, and an examination of the potential associations between clinical management and outcome of CABM and MS. Identifying and recommending changes that have the potential of preventing these conditions and improving the outcome when they occurred, is a central aim of this research.

The thesis is structured as follows:

Following this Introduction, Part 1, Chapter 2 - Background to bacterial meningitis, covers a synthesis of the existing published literature on CABM and MS from regions with a similar context to that of the UK, including demographic, cultural and health system. Included with this is a brief overview of the history and recognition of meningitis in the health arena; its epidemiology world-wide; a brief account of its pathology and microbiology; and a background to, both, clinical and public health management of these conditions. I then argue the rationale for this study and introduce the aims and objectives of this research.

Chapter 3 presents the data and methods used in this research. Including a detailed account of: the background of the available data sources used, the specifics of this data, the collection of new data, the epidemiological approaches used, and the statistical methods and analysis undertaken.

Part 2 presents, separately, the results and findings of the research I undertook to address the first four objectives. The last objective that relates to generating

recommendations for improved prevention and management of CABM and MS is presented in Chapter 9, following discussion of my findings in a broader context in Chapter 8.

Understanding the epidemiology of any condition, in this case of CABM and MS, is the first step in any examination of policies for management or prevention of the condition. I have undertaken a detailed analysis of the epidemiology of CABM and MS using the available routine surveillance data for the causative forms of CABM and MS. I have examined the potential changes in the epidemiology of CABM and MS in terms of time-trends but also demographical and geographical differences. I have also presented and discussed these findings in context of prevention policies in England and Wales in Chapter 4.

To examine and quantify the potential uncertainty and inaccuracy of the reports within the routine surveillance data I have used the available data on incidence and mortality associated with pneumococcal meningitis, applying a capture-recapture method. Chapter 5 presents this work, which is not only an examination of the methodology of capture-recapture in this context, but also a consideration of the implications of these findings for the practice and policy in England and further a field.

Clinical management of CABM and MS is clearly the most important issue when the disease has occurred, i.e. when an individual is affected. Chapter 6 present a retrospective review of clinical management in randomly selected hospitals across England and Wales. The characteristics of the hospitals, the patients, and the diagnosis and treatment of them is presented. The diagnosis and treatment, referred to further on in this thesis as clinical management, will be assessed against the then current guidelines published by the British Infection Society (BIS).

In Chapter 7, I examine the potential associations of clinical management indicators with the outcome of CABM and MS. I also focus on assessing and comparing

different statistical methodologies used in examinations of risk factors in clinical practice, with particular focus in dealing with missing data and controlling for confounding in observational clinical management studies.

All the results chapters (Chapter 4 to 7) include a short background to the issue, brief mention of the methods and the data used, results and a concise discussion of the strengths and limitations of that particular study.

Chapter 8 discusses the findings of my research, in relation to the strengths and weaknesses of the study, linking my work to previous published relevant research, and in context of health policy in England and Wales. Based on the above I then present the recommendations, in Chapter 9, to be implemented to improve the prevention and management of bacterial meningitis in England and Wales. Finally, I discuss what I consider should be done to take the findings and recommendations from this research further.

1.5 Short title

The research for this thesis has been known with the short title of "Bacterial meningitis amongst adults". This title is used as heading throughout the thesis document; it has been used in much of the correspondence for the research, and sometimes at the different forums.

1.6 Contributions

The initial project proposal was written by my external advisors: Prof R Heyderman, the Principal Investigator (PI) of the study; Prof J Stuart, co-investigator, and Prof K Cartwright, Co-investigator. The proposal was for reviewing the clinical management of bacterial meningitis amongst adults in England and Wales, submitted to the Department of Health (DH). A copy of this proposal is included in Appendix 1.1.

I was the research fellow for this study, and had the responsibility for developing and undertaking the study, including: recommending to the PI appropriate members for the Expert Panel; developing the standards and indicators, studying case-report forms; establishing contact and enrolling hospitals; collecting, maintaining and managing the data; generating appropriate questions for the study, analysing the data, writing up reports and papers for publication; identifying and developing appropriate forums for presentation, publication and dissemination.

Having taken the research fellow post and inherited the initial project proposal to the DH, I developed the full study protocol for the review of the clinical management; including the study design and protocol for the statistical analysis. I worked with the support of the study statistician, Mr. Tom Nichols, who was member of the Expert Panel for the national review of clinical management. His specific support was to help calculate the study sample, organise the data for analysis, merge the data on clinical management with hospital size and coverage population; weighting the data based on the annual reported number of cases of CABM and MS per regions, support around calculations and definitions of variables measuring time to a clinical management indicator and measuring the severity of illness.

I held the ultimate responsibility for the data management and analysis and was solely responsible for the choice of which analyses to undertake, running the analyses in appropriate statistical software, choosing definitions and tests to be used to interpret, the results.

I generated the research questions, identified the data sources, developed the study protocols and analysis as well as conducted the analysis for the other three parts of the original research within this thesis, including: the epidemiological review, the capture-recapture analysis and the examination of the association of the clinical management indicators with the outcome of CABM and MS.

My main external advisor, Prof R Heyderman, closely and regularly supervised and advised on my work throughout the research. He was the PI for the review of the clinical management study, and as such advised and assisted when needed in the process of recruiting the Hospital Trusts. Prof R Heyderman was also mainly responsible for steering the overall direction of the study.

Prof R Heyderman and Prof Stuart contributed to the formulation of the research question for the review of the epidemiology and the risk factors studies. They both supervised and advised on the strategies and results of the analysis of all the studies; and contributed to the writing of the peer-review publications resulting from these studies.

Prof D Lawlor supervised and advised on my work throughout the research as needed, focusing on advice around the epidemiological rigor of the studies undertaken and interpretation of the results. Prof D Lawlor also contributed to the writing of the peer-review publication on the review of the epidemiology.

The Internal supervisors, Prof P Farrington and Dr K McConway, advised me regularly on the overall direction of the PhD research. Specifically advising on the statistical strategies and methods undertaken or considered for the studies I undertook throughout this research.

The part of the research which was funded by the DH to review the clinical management of CABM and MS was steered by a panel of experts in the different fields relevant to the study. The Expert Panel (EP) included: a General Physician (GP), an infectious disease consultant, an epidemiologist, a public health consultant, a paediatrician and a statistician. The role of the EP was to regularly oversee the design, data collection, analysis and recommendations to the DH. The EP also contributed to the writing of the report and peer-review publication for this study. The list of the EP members and their affiliations at the time of the study is included in Appendix 1.2.

1.7 Publications resulting from this research

Peer-reviewed:

The following peer-reviewed publications, in order of relevant parts appearing in the thesis, have resulted from my research:

Gjini, A. B., Stuart, J. M, et al. (2006). "Changing epidemiology of bacterial meningitis among adults in England and Wales 1991-2002." Epidemiol Infect 134(3): 567-9.

Gjini, A., Stuart, J. M., et al. (2004). "Capture-recapture analysis and pneumococcal meningitis estimates in England." Emerg Infect Dis 10(1): 87-93.

Gjini, A. B., Stuart, J. M., et al. (2006). "Quality of in-hospital care for adults with acute bacterial meningitis: a national retrospective survey." Qjm 99(11): 761-9.

Not peer-reviewed:

Hartman, G.C., Gjini, A.B., and Heyderman, R. (2004). "The emergency management of adult bacterial meningitis." Acute Medicine, CPD journal 3(2):53-8.

Chapter Two

Background

Chapter Two - Table of content

2.1 Introduction to this chapter

This aim of this chapter is to set the scene for the research that I carried out and to acquaint the reader with the importance of adult CABM and MS for the population of England and Wales. The information presented here is primarily based on a review of the published literature; however my critical understanding of this literature has a role in the way it is interpreted here.

I start by briefly describing the literature search approach and give a brief account of the relevant historical developments in the occurrence and management of meningitis. Followed by a description of the global epidemiology and where it is relevant to England and Wales.

The microbiology and pathology of the disease is essential to the epidemiology and management and I will therefore give a brief review of both. A background of the clinical presentation and management; and the existing public health recommended practice then follows. This is accompanied with a background to the reporting and surveillance of this disease and the current prevention strategies for CABM and MS, including chemo and immuno-prophylaxis.

2.2 Literature search

The available literature was reviewed to appraise and synthesise evidence on disease epidemiology, management guidelines, and current practises in diagnosis and management of bacterial meningitis and meningococcal septicaemia. Major electronic databases of peer reviewed scientific literature were searched for relevant publications, as well as other sources of publications, i.e. DH, UK and CDC, US. The review will especially focus on existing literature concerned with adult population.

2.2.1 The search strategy

To inform this chapter I searched published literature on the relevant topics as follows.

i) Definition of the topic

The research, and therefore the literature used include the areas of: epidemiology of meningitis; disease presentation and management, health policy and relevant epidemiological and statistical methods.

Within the disease presentation and management the main issues considered are concepts of different forms of bacterial meningitis and meningococcal septicaemia, diagnostic procedures related to acute severe infections in general and meningitis in particular, treatment and management, as well prophylaxis and prevention strategies.

ii) Scope and boundary

The focus of the research is meningitis and meningococcal septicaemia among adults in England and Wales. However, there are a few aspects of this that can be generalised further, such as: 1) the early clinical presentation of a meningitis case is often the same as of other serious infections and hence its clinical management is similar. 2) the literature reviewed reflects the studies and evidence across the globe, therefore this research can be generalised and applied to any countries with similar epidemiology of the disease, demographics of the population, context, and provision of health care and prevention.

iii) Data sources

I have used various electronic databases; libraries located within University of Bristol and Open University; proceedings of conferences; recommendations from experts in the field, the Internet and others, to find the relevant information.

2.3 A brief history of meningitis

It is important to note that in literature the term 'meningitis' often, if not specified otherwise, refers to meningococcal meningitis, with or without septicaemia. This is primarily because the other common causes of bacterial meningitis, such as Hib and *S. pneumoniae* present in greater proportion as other forms of infection including ear, throat infections, pneumonia and sepsis. Whilst, meningococcal infection almost exclusively presents as meningitis and meningococcal septicaemia it is usually described as meningococcal disease (MD).

2.3.1 Recognition of meningitis

Meningitis as a clinical presentation is probably as ancient as the human race. The first known description of meningitis is, however, thought to date back to the Greek philosopher, Hippocrates, around the 15th Century BC. There are records accounted to Hippocrates that refer to meningitis: "if during a fever the neck is twisted ... it is a fatal sign". However, it is probably Avicenna in "The Canon of Medicine" at the beginning of the 10th Century who gives the first most accurate and detailed description of meningitis; indeed some argue that Avicenna's description is almost as accurate and relevant today as it was 1,000 years ago (Skinner 2001).

The actual term 'meningitis' is thought to have had been first used by the British doctor Thomas Willis (1621–75) in 1661 (Williams and Sunderland 2001), whereas, in the United States, the disease was first described in Medfield, Massachusetts, by Danielson and Mann in 1806. Subsequently, the disease referred to as 'malignant spotted fever' continued to be reported in the medical journals of the time (Grady 1965). The first epidemiological study on the disease was reported in a dissertation work for a medical degree by Nathan Strong in 1810 (Scriabine 2003) who strongly suggested that there may possibly be more then one form of 'spotted fever', he goes on to acknowledges himself as being "profoundly ignorant". It is also interesting to

note that Strong attempts to describe that clinical presentation as dual, i.e. in the form of meningitis – with "stiffened and spasm of extensors muscles of the head and the neck" and in the form of septicaemia – with "spots and heat of the skin up to and rarely above the natural temperature" (Strong 1810).

Meningitis' potential for outbreaks is now well acknowledged, but the first description of an MD outbreak is thought to be from Geneva, Switzerland, probably in the early 19th Century, c.1805 (Vieusseux 1806). Around that time Strong, also, noted the disease's potential for sporadic or outbreak occurrence (Strong 1810). The literature shows that the outbreak pattern of MD continued throughout the 19th and 20thC in Europe, with a fatality of 75 to 80% of affected people (Segall and Pollard 2006).

The cause of the disease, though, remained unknown and even the contagious nature of the disease was not acknowledged until the late 19th Century; understandingly so, as it is generally transmitted by healthy carriers, and is not as contagious as other infections recognised at the time, e.g. typhoid fever (Grady 1965). In 1887 Anton Weichselbaum reported to have discovered the causative organism of cerebrospinal meningitis, which he named Diplococcus intracellularis meningitides (Weichselbaum 1887; Yazdankhah and Caugant 2004).

The two other major causes of bacterial meningitis, *Haemophilus influenzae type b* (Hib) and *Streptococcus pneumoniae* are not quite so distinctly described as causes of meningitis. This is probably because they are major causes of other clinical manifestations, including upper and lower respiratory tract infections, and therefore described in conjunction with these clinical manifestations of infection with these bacteria.

Streptococcus pneumoniae is reported to have been first isolated in 1881, simultaneously and independently by two scientists in the U.S. Army physician George Sternberg and the French chemist Louis Pasteur. The organism was renamed *Streptococcus pneumoniae* in 1974.

Hib was isolated during the 1889 influenza pandemic by Dr Richard Pfeiffer and was then thought to be the cause of Influenza. Only in the early 1930s it was recognised that this bacteria was a secondary infection, not the cause of influenza.

2.3.2 Treatment

In the 19th and early 20th centuries, i.e. in the pre-antibiotic era, the treatment of infections was mainly treating the symptoms, and at best using an appropriate animal or human serum. Stimulants (wine, brandy, etc) and opium were the treatments of choice, though the use of evacuants – blood release and emetics, was debated by some.

Regarding the use of serum, for treatment of and protection from pneumococcal infection, serum from rabbits immunized against pneumococcus or from humans was recognised in the early twentieth century (Brown 1910). In 1913, Simon Flexner (1863-1946) was the first to report success in treating bacterial meningitis with intrathecal equine meningococcal antiserum. He reported that amongt 1300 patients with epidemic meningitis treated the mortality was reduced to 31 percent (Flexner 1913; Flexner 1913).

Discovery and consequently the use of penicillin in 1944, and the sulphonamides only a few years before, dramatically improved the outcome of patients with meningitis (Rosenberg and Sylvester 1944; Rosenberg and Arling 1984). The case-fatality with the use of penicillin dropped from up to 90% with no treatment to around 40% (Dowling, Sweet et al. 1949; Dowling, Sweet et al. 1949).

With the continued use of, but also further developments in, antibiotics, penicillin has been replaced, either because of resistance to, or simply because of increased effectiveness against a wider range of bacteria, with other antibiotics, e.g. most recently the 3rd generation cephalosporins.

2.3.3 Vaccination

Meningococcal

In 1978 the first polysaccharide vaccine to protect against meningococcal meningitis was introduced in the US (Grabenstein 1997). The vaccination programme was extended to small children, however one of the serious limitations with polysacharide vaccines was the lack of immunity generated in children under 2. In the early 1990's the medical community recognised that teenagers and young adults were at increased risk for meningococcal disease. In the late 1990s the relevant governmental bodies in the developed countries, including the Department of Health UK, the American College Health Association (ACHA), and others recommended that colleges and universities should inform all new students about the risk of meningococcal disease; and offer vaccination (Fischer, Hedberg et al. 1997; Neal, Nguyen-Van-Tam et al. 1999). However, the cost-effectiveness of this strategy has been debated (Jackson, Schuchat et al. 1995).

Development and licensing of meningococcal conjugate C vaccine in the late nineties provided improved benefits for control of meningococcal vaccine. In 1999 England became the first country to undertake a national vaccination campaign for teenagers with Meningococcal C Conjugate vaccine (Men C) to be followed as part of the routine childhood vaccination. Meningitis C then accounted for 36% of all meningococcal cases. In May 2008 the Health Protection Agency (HPA) reported 0 deaths from meningococcal C. HPA figures show that there were only 13 cases of Meningitis C in 2008/09 compared to 955 in 1998/99 - a decline of 99% largely due to the use of meningococcal C vaccine (HPA 2009).

Pneumococcal

With regard to pneumococcal vaccination, the efficacy of immunisation against the pneumococcus was first demonstrated in South African miners in the early 20th

Century (Wilson 1972). In 1930 it was learned that carbohydrate molecules on the surface of the pneumococcus are important contributors to immunogenicity and in 1936, a pneumococcal capsular polysaccharide vaccine was used to abort an epidemic of pneumococcal pneumonia (Butler, Shapiro et al. 1999; Ortqvist 2001). The polysaccharide vaccine has had, continues to have, a wide-spread use amongst the older people though effectiveness is uncertain. Recently there has been introduction of pneumococcal conjugate vaccine I various countries around the world, in the UK it was introduced in the childhood vaccination programme in 2006 (CMO Letter 2006). Nonetheless, invaisve pneumococcal disease still remains the leading couse of death in children world-wide, causing more deaths than malaria and HIV together.

Haemophilus Influenzae Type b

In the 1970s the first polysaccharide vaccine against *Haemophilus influenzae type b* was in use but, as with other polysaccharide vaccines, it had limited effectiveness in children under 2 years old, the age-group most at risk. In 1985 the first polysaccharide vaccine was licensed for the under 18 month's olds, but still effectiveness was not high.

In 1987 the first conjugate Hib vaccine was licensed, and began to be rolled out as a national vaccination in many countries in the early 1990s. Nonetheless, Haemophilus infections even today remain a leading cause of illness and death among children worldwide causing around 700,000 deaths a year

(http://www.hibdisease.com/hib2005professional.swf).

2.4 A brief background on the global epidemiology of meningitis

2.4.1 Overview

Bacterial meningitis and meningococcal septicaemia cause a significant morbidity and mortality world-wide (Apicella 2005). These are serious and potentially life-threatening conditions with over 10% fatality and 30% long-term sequelae despite the availability and use of potent antibiotics. Until a few decades ago major epidemics occurred across the globe, and still do so generally in the poorer regions of the world, such as sub-Saharan Africa (Greenwood 1999; Apicella 2005; Greenwood 2006; Boisier, Mainassara et al. 2007).

It is difficult to measure the numbers of cases and deaths, primarily due to multiple causation (meningococcus, pneumococcus, Hib, etc), but it is estimated that numbers world-wide are in the millions for cases and hundreds of thousands for deaths (Quagliarello and Scheld 1992; Adegbola, Usen et al. 1999). The disease affects all populations and age groups, but is most common in children under 5 and in the 'Meningitis belt'. Despite the parenteral antibiotic, and further, treatment the outcome of these conditions still remains grave. About 15-20% of adult cases die and a further 30% suffer long-term sequelae (Greenwood 1984; Durand, Calderwood et al. 1993; Stanek and Mufson 1999).

Several reviews have characterised the epidemiology of each of the main causative bacteria separately (Abbott JD 1985; Bijlmer 1991; Miller, Waight et al. 2000; Cartwright, Noah et al. 2001). There are relatively few reviews of the global epidemiology of bacterial meningitis (Schwartz, Moore et al. 1989). The reviews of the bacterial meningitis, inclusive of causative organism, usually are restricted to a defined population, either geographical, or age-related (Fortnum and Davis 1993; Urwin, Yuan et al. 1996; Gold 1999; Rosenstein, Perkins et al. 1999; Spanjaard, van der Ende et al. 2000). Even though the disease is much more common and graver in

the less developed world, namely Africa, most of the published research, however, comes from the western developed countries. Another point is that commonly in published literature the term 'meningitis' is used unspecified. As mentioned above, most often in such cases the authors will refer to Meningococcal meningitis; generally because the other causative organisms present with other forms of invasive disease more often then as meningitis (Jolly and Stewart 2001).

I will analyse and interpret in greater detail the current and changing epidemiology of the CABM and MS amongst the adult population in England and Wales, further in this thesis (Chapter 4), but here I will give a brief background of the global epidemiology of CABM and MS.

2.4.2 What are the factors that influence the epidemiology of meningitis?

Although factors that are considered to increase the risk of meningitis and MD in humans, to some extent, are not well understood, it has been documented that the individuals' susceptibility, poor living conditions, and introduction of new pathogenic strains, are associated with a higher risk of disease. The epidemiology of the disease is determined by several factors, and these can broadly be grouped into:

- the characteristics of the pathogenic agent;
- the host factors;
- socio-economic; and
- environmental factors

2.4.2.a The characteristics of the pathogenic agent

These are of great importance in the epidemiology of the disease. The bacteria that are responsible for most cases of meningitis are effective at colonising the human nose or throat. Some strains have higher pathogenicity or virulence, i.e. the ability to cause disease as opposed to mild or asymptomatic infection. The ability of the

agents to survive in the environment is also of great importance, and most of the CABM causes survive only for short periods outside the body i.e. require close and direct contact with the aerosols from the infected person for transmission. However, *M. tuberculosis* can survive for long periods in the environment, and *L. monocytogenes* is generally transmitted through the oro-faecal route. Capsulated bacteria display higher pathogenicity, i.e. *N. meningitidis, S. pneumoniae* and *H. influenzae* type b.

2.4.2.b Host factors

These are mostly related to immunity of the host, and specifically humoral and local immunity (such as mucosal, both respiratory and digestive). As mentioned above, for most causes of CABM, apart from *L. Monocytogenes*, the route of infection is droplets or aerosols and the port of entry is the upper respiratory tract, hence a damaged respiratory mucosa is thought to increase the risk of invasion. For example, it is thought that during the dry season, particularly in the meningitis belt, the mucosa is more fragile and offer less effective prevention. Similarly the effect of smoking in an increased risk of infection is partially explained by damaged mucosa (Stuart, Cartwright et al. 1988; Fischer, Hedberg et al. 1997).

Several reports have also suggested that having flu and/or another respiratory infection increases the risk of meningitis by up to four times (Cartwright, Jones et al. 1991) . People who have compromised humoral immunity, e.g. HIV infected, long-term conditions, cancers, long-term treatment with corticosteroids, etc, are at increased risk of infection.

2.4.2.c Socio-economic factors

Poverty, overcrowding, and poor living conditions have been well established as a risk factors for meningitis (Baker, McNicholas et al. 2000). Historically there have been major epidemics following major social disruptions, like the first and second

World Wars. More recent and perhaps more localised humanitarian emergencies have been associated with local or regional outbreaks (Santaniello-Newton and Hunter 2000; IRC 2002; MSF 2005). Therefore one of the first public health measures in such circumstances is vaccination against forms of bacterial meningitis (WHO 2001).

In normal social circumstances, and frequently in the developed countries, it is rather different social factors. Commonly it is amongst teenagers and young people who attend crowded venues, for example night clubs, that present an increased risk of infection with CABM and MS (Cookson, Corrales et al. 1998; Finn, Groves et al. 2001; Harrison, Pass et al. 2001). The health-care system, as mentioned above, access to health care facilities, but also provision of prevention programmes, such as vaccination influence greatly the epidemiology of the disease (Molesworth, Cuevas et al. 2002).

2.4.2.d Environmental factors

In the African meningitis belt epidemics occur following periods of very low humidity and dusty conditions, it tends to die-off with the onset of the rains. This suggests that environmental factors also have an important role in the epidemiology of the disease (Greenwood, Blakebrough et al. 1984; Besancenot, Boko et al. 1997; Greenwood 1999; Molesworth, Thomson et al. 2002). A recent study on the spatial distribution and spatial forecasting of meningitis epidemics in Africa indicated that absolute humidity, land-cover types (savanna, urban, grassland, dryland, forest wetland, etc) and population density are associated with areas with high and low risk of epidemics (Molesworth, Cuevas et al. 2003).

In the northern industrialised countries, like the UK, outbreaks usually occur during winter times, December through to February. Although relative humidity is high, the absolute humidity is lower (Millon 1989).

2.4.3 Which are the most common causative agents of meningitis?

Causative organisms of CABM and MS are numerous, and vary according to the geographical region and age-groups, nonetheless there are a few that are commonly more prevalent and relevant in England and Wales, including:

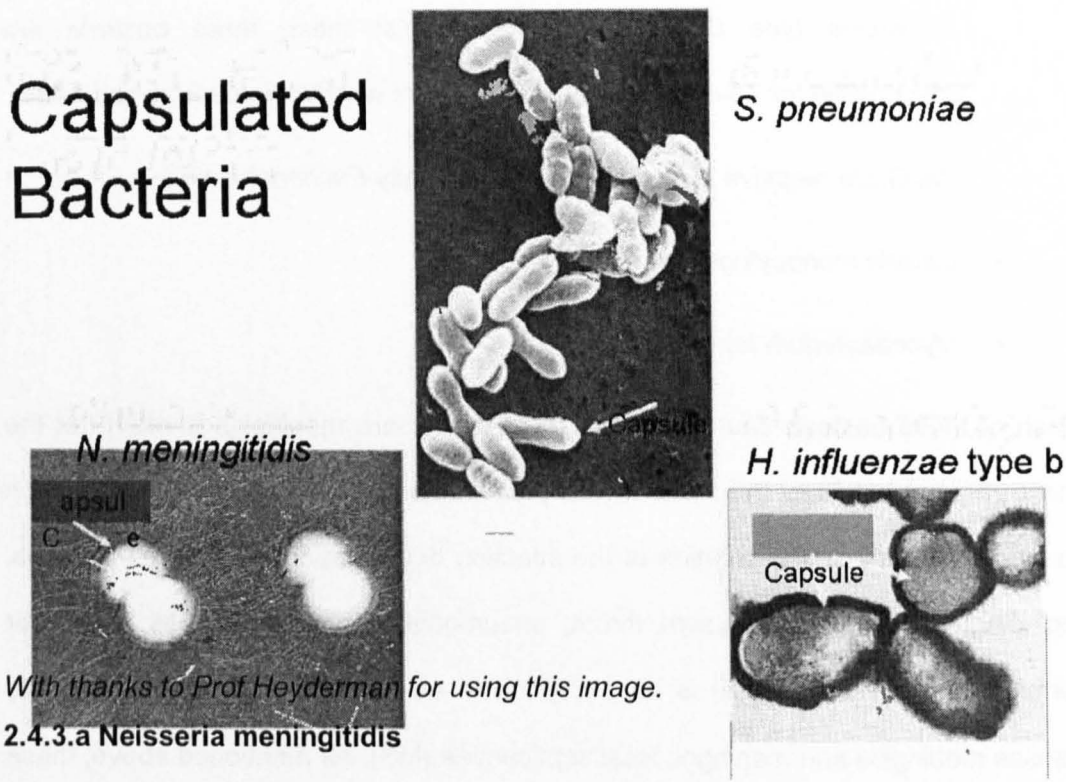
- the capsulated bacteria: *Streptococcus pneumoniae, Haemophilus influenzae type B, Neisseria meningitidis*; these three bacteria are responsible for 75-85% of all cases of CABM worldwide (Greenwood 1984)
- the Gram negative enterococci, predominantly *Escherichia coli;*
- *Listeria monocytogenes;* and
- *Mycobacterium tuberculosis.*

Each of these bacteria causes various diseases, where meningitis is often not the most frequent but likely the most severe presentation of the infection. The common forms of the clinical presentation of the infection being upper respiratory infections, including: otitis media and sore throat; pneumonia; sepsis; meningitis and other forms. *Neisseria meningitdis* is an exception in as much as it almost exclusively causes meningitis and meningococcal septicamiae (MS). As mentioned above, these two manifestations often occur jointly and known with the term Meningococcal Disease (MD). The clinical presentation and the pathology of CABM and MS will be reviewed further in this chapter.

Because of many overlapping, but also varying features in epidemiology, pathology, clinical presentation and management of the common causes of CABM and MS it is difficult to review the epidemiology of CABM and MS as a unique condition globally or to follow a logical and structured approach in one review. After several attempts of various outlines, I decided to follow the 'Agent - Host - Time - Place' framework for each of the pathogens reviewed in this research.

The capsulated bacteria, *N.meningitidis*, *S.pneumoniae* and Hib (Figure 2.1) are the most common forms of CABM, though with the implementation of the conjugate vaccines, Hib and Men C, and recently *S.pneumoniae*, their burden is reducing significantly.

Figure 2.1 - Capsulated bacteria, common causes of CABM.



With thanks to Prof Heyderman for using this image.

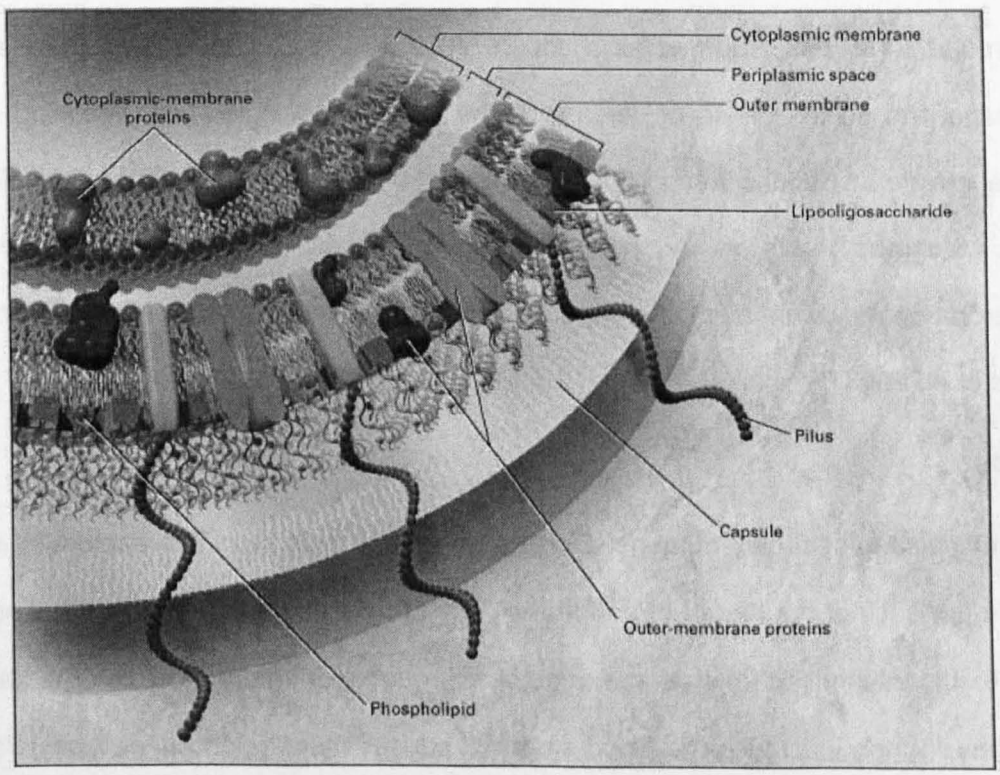
2.4.3.a Neisseria meningitidis

The agent

Neisseria meningitidis (*N. meningitidis*) is a gram negative diplococcus. The major outer membrane components of the bacteria, capsular polysaccharide, outer membrane proteins, and lipo-oligosaccharide (endotoxin) are linked to the ability of meningococcus to be virulent to the humans. There are 13 serogroups of *N. meningitidis* based on different capsular polysaccharide structures, but only 6 (A, B, C, W-135, X, and Y) cause the most life-threatening disease *(Rosenstein, Perkins et al. 2001)* .

The immunotype is determined by the differences in lipo-oligosaccharide (12 imunotypes, i.e. LI-L12), whilst the serotype (20 groups, e.g. 1, 2a, 2b, 21) and serosubtype (10 groups, e.g. P1.1, P1.2 to P1.16) are identified by differences in the outer membrane proteins (Verheul, Snippe et al. 1993; Raymond, Reeves et al. 1997; Dolan-Livengood, Miller et al. 2003)

Figure 2.2 - A cross sectional view of *N. meningitidis* taken from: D. S. Stephens, B. Greenwood, et al. Lancet. 2007.



Epidemic meningococcal meningitis occurs in many parts of the world but the largest and most frequently recurring epidemics have been in the area of sub-Saharan Africa where a recent pandemic was associated with attack rates exceeding 500 per 100,000 and thousands of deaths. In this region, commonly referred to as the meningitis belt, meningococcal disease presents predominantly as meningitis alone (Molesworth, Thomson et al. 2002).

In the Americas and Europe serogroup B is the predominant agent causing systemic disease, followed in frequency by serogroup C. Serogroup C has caused relatively higher fatality associated with both clusters or local outbreak to larger outbreaks (Brooks, Woods et al. 2006). Serogroup A meningococcus was historically the main cause of epidemic meningococcal disease globally and still predominates in Africa and Asia. Generally, serogroup B is responsible for most sporadic cases; serogroup C causes large or small outbreaks (De Wals, Hertoghe et al. 1981; Cooke, Riordan et al. 1989).

Serogroup W-135 has emerged as a cause of outbreaks associated with the Hajj pilgrimage and as the cause of disease in the African meningitis belt, including a large epidemic in Burkina Faso (Aguilera, Perrocheau et al. 2002). Since the mid 1990s, serogroup Y has caused increased rates of disease in the USA and Israel, and serogroup X has caused local outbreaks in parts of sub-Saharan Africa (Djibo, Nicolas et al. 2003; Nicolas, Djibo et al. 2006).

The host

N. meningitidis infects only humans; there is no animal reservoir. The bacterium is found in the back of the throat, of about 5 to 30% of healthy people, normally called carriage. It is transmitted from person to person through respiratory droplets or throat secretions. When it invades the blood-stream it causes meningococcal septicaemia and /or meningitis. Usually septicaemia is the more dangerous clinical syndrome, causing a higher fatality (Thomson and Riordan 2000). World-wide MD accounts for around 500,000 cases and 50,000 deaths per year (World Health Organization 1998). Up to 20,000 deaths are reported from the sub-Saharan African countries only.

All ages are affected but young children, under 5, and teenagers are at highest risk of the disease (Harrison, Pass et al. 2001). People living in crowded conditions are also

at higher risk. The clinical manifestation is either meningitis, which generally has a lower case fatality rate, or septicaemia, or the combination of both (Peltola 1983).

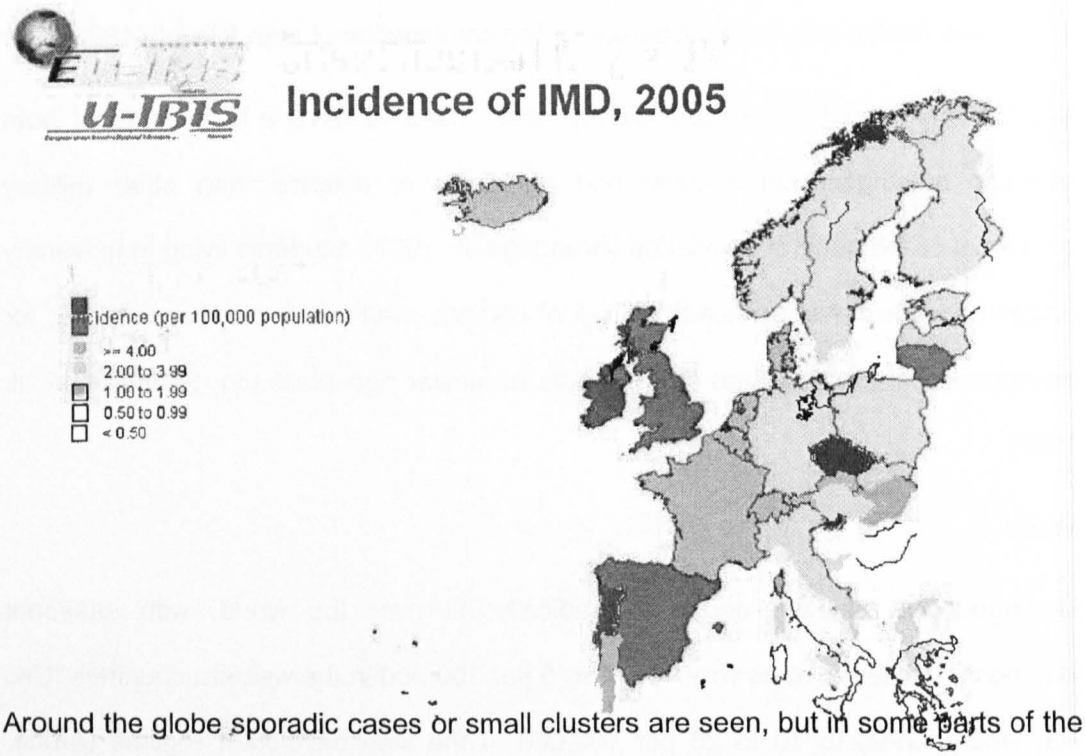
New military recruits have consistently been found to have a higher risk of both sporadic meningococcal disease and outbreaks of disease than other military personnel or the general population (Brundage JF 1987). Students living in university accommodation have an increased risk of disease, perhaps for similar reasons, for meningococcal disease than other people of similar age (Jackson, Schuchat et al. 1995).

Place

Meningococcal disease occurs sporadically all over the world, with seasonal variations. Incidence rates vary from 1 to 5 per 100,000 in the western countries (UK, US, Netherlands) to 10 to 25 per 100,000 in the less developed regions (Africa, Asia). In Europe, North America and Africa meningococcal meningitis is common and dominant form of CABM; but much less common in South East Asia (Chiou, Liao et al. 2006).

In the UK *N. meningitidis* is the main cause of CABM and MS and the incidence is relatively high compared to other European countries.

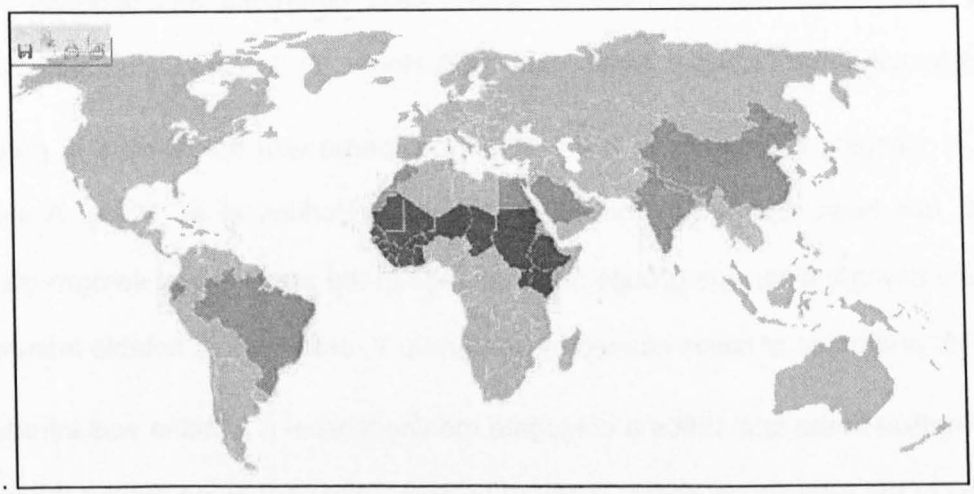
Figure 2.3 - Incidence of meningococcal disease in Europe. Source EU – IBIS 2007.



Around the globe sporadic cases or small clusters are seen, but in some parts of the world, like the meningitis belt, large outbreaks are common. During the epidemics, the attack rates are as high as 100 to 500 per 100,000 (Schwartz, Moore et al. 1989). In Europe, the Americas, Australia, and New Zealand generally *N. meningitidis* serogroups B and C are the most common cause of disease and tend to occur more frequently in winter and spring. Whilst in Africa and Asia it is serogroup A which is the main cause of disease and, as mentioned above, often causes large epidemics regularly across the meningitis belt.

For the successful control of MD globally the crucial challenge will be effective introduction of new meningococcal vaccines into developing countries, especially in the meningitis belt of sub-Saharan Africa, where they are urgently needed (Tikhomirov, Santamaria et al. 1997). A new conjugate meningococcal A vaccine (MenA) is on trial through the Meningitis Vaccine Project (MVP) (Hodgson, Forgor et al. 2008).

Figure 2.4 - World map of outbreak regions of MD.



Legend: Outbreaks are common ■ Sometimes there are outbreaks ■

Generally sporadic cases ■

Time

Seasonal pattern As mentioned above, MD has a regular seasonal pattern of occurrence, being at highest peak during the dry-seasons, and in winter in Europe and North America. Due to herd immunity (whereby transmission is low when a relevant percentage of the population has acquired immunity due to disease or vaccination), the epidemics in the meningitis belt occur in a cyclic mode. The role of climatic factors is not well understood; but it is thought that the effect is probably in minor damages made to the respiratory mucosa, facilitating thus the invasion by the bacteria.

Changing epidemiology

New strains As recently as throughout the 1960s, 70s and 80s *N. Meningitidis* caused pandemics spreading in about 30 countries around the world caused mainly by the group A. More recently, other groups, such as W135 and serogroup X have been cause of major outbreaks, particularly so in he western countries (Djibo, Nicolas et al. 2003; Nicolas, Djibo et al. 2006). In 2000, a large outbreak caused by *N.*

meningitidis group W135 occurred during the Muslim pilgrimage in the Hajj; and since then W135 has continued to cause small outbreaks and sporadic cases throughout the world (Singer, Maur et al. 1980, Hahne, S. J., Gray, S. J., et al. 2000).

Age A changing epidemiology in the 1990s compared with the disease in previous years, has been reported in the US (Rosenstein, Perkins et al. 1999). A shift of disease towards older age groups and a change in the predominant serogroups with a higher proportion of cases caused by serogroup Y, are the most notable features.

Vaccination In the late 1990s a conjugate meningococcal C vaccine was introduced in most of the western countries, followed by some other countries around the world. This has had a big impact in the epidemiology of MD around the world, with a dramatic decrease in incidence of group C close to elimination (Trotter, Andrews et al. 2004).

2.4.3.b *Haemophilus influenzae*

The agent

Haemophilus influenzae type b, or Hib, is a capsulated bacteria which is a major cause of morbidity and mortality around the world and is responsible for most of bacterial meningitis (Peltola 2000; Uduman, Adeyemi et al. 2000). It is a common pathogen in adults, often causing meningitis (Strausbaugh 1997).

The host

It is estimated to cause about 3 million serious illnesses and close to 400 000 deaths per year, primarily due to meningitis and pneumonia. The most at risk are children under the age of 5, with those between 4 and 18 months of age especially vulnerable (Bijlmer 1991). Treated early, it has a fatality rate of under 10%, but up to 30% of patients who recover suffer residual neurological effects. In the UK it has been one of the most common causes of meningitis, in the pre conjugate vaccine era (Urwin, Yuan et al. 1994).

Place

Until the implementation of the conjugate vaccine Hib was the most common of bacterial meningitis, in Europe as well as in USA, Southern Pacific, including Australia and New Zealand.

The infection is wide-spread with highest incidence rates reported from the poorest countries, rangingi from 95 to less then 10/100,000 in under 5s in population without conjugate vaccine programmes (Gessner 2002); however these reports are strongly subject to the ascertainment differences between the developed and developing countries.

Hib invasive disease, and meningitis in particular, is most common in developing countries, estimated to cause 3 million cases of serious illness (mainly pneumonia and meningitis) in children under 5 years of age each year and about 400,000 deaths (Adegbola, Usen et al. 1999).

Time

Since the early 1990s, due to the introduction of the Hib conjugate vaccine into the childhood vaccination programmes, the disease has been almost eradicated from Western Europe, North America, Australia and New Zealand (Peltola 2000). Until the introduction of the HiB conjugate vaccine Hib accounted for over 50% of all meningitis cases in Europe. However, the disease still represents a large burden in the developing world, causing hundreds of thousands of needless deaths every year and leaving 15 to 35% of survivors with permanent disabilities. By November 2006 about 106 countries had introduced the Hib conjugate vaccine into their childhood vaccination programmes. And only 26 of 72 resource limited countries have introduced Hib vaccine or are approved by GAVI to introduce Hib soon.

2.4.3.c *Pneumococcal meningitis*

The agent

Streptococcus pneumoniae (the pneumococcus) is a Gram positive capsulated diplococcus that causes a range of invasive disease, including sepsis and pneumonia as the common ones. Meningitis is the presenting diagnosis in about 10% of cases of invasive disease but is usually the most serious form of the infection.

The host

Young children and then older adults are most often affected, especially the under 5s and over 65s (Butler and Schuchat 1999; Wasier, Chevret et al. 2005). Pneumococcal infections represent the leading cause of vaccine-preventable deaths. Around 40% of all adults and children, healthy or otherwise, carry the pneumococcus in their nasopharynges. This disease often infects young children and the elderly.

The case fatality rate for pneumococcal meningitis remains high, as high as 30% especially amongst the very young and very old (Butler and Schuchat 1999), but fatality remains high for other IPD as well (Feikin, Schuchat et al. 2000).

Time

There has not been any significant change in the epidemiology of pneumococcal meningitis (or the IPD for that matter) in recent times (Laurichesse, Grimaud et al. 1998). A slight rise in incidence of IPD overall has been reported from some Western countries, mainly attributed to an increase of the disease in the elderly (Ortqvist 1999).

The biggest change, however, has been in the increasing incidence of antibiotic resistant strains in *S. Pneumoniae* isolates, both blood and CSF. Although the rates of resistance in England and Wales is reported to be lower than in some other Western countries, they have been in an increasing trend, nonetheless (Laurichesse, Grimaud et al. 1998).

Until the mid 2000s the vaccination policies did not change significantly the epidemiology of pneumococcal meningitis. The polysaccharide vaccines have been in use throughout the world, but offering protection to adults, generally, and have had no or little effect in children less than 5 years of age and do not prevent carriage without symptoms. Lately, with the introduction of the conjugate pneumococcal vaccines, there has been a significant drop in the rates of disease amongst children, a decrease in carriage rates, an increase in herd immunity, and a decrease in rates of antibiotic resistant strains (Cartwright 2002; Hennessy, Singleton et al. 2005; Kyaw, Lynfield et al. 2006). Another significant effect of the PCV on the epidemiology of the pneumococcal meningitis and overall IPD, has been on the serotype switching, ie since the introduction of the PCV proportionately more disease is caused by the non-vaccine serotypes. In the UK a seven valent conjugate vaccine (PCV7) is in use, and in the last few years reports through active and enhanced surveillance of all pneumococcal infections show that the serotypes not included in the vaccine are becoming more prevalent (Kaye P, Malkani R, *et al.* 2009; Albrich, Baughman *et al.* 2007; Hsu, Shutt et al. 2009).

Place

Pneumococcal meningitis is most common in sub-Saharan Africa; but is also common in South East Asia where it account for almost one third of all CABM cases (Chotmongkol and Techoruangwiwat 2000). In Europe, including the UK, and the United States, *S. pneumoniae* is the most common community acquired bacterial pneumonia and meningitis, estimated to infect over 100 per 100 000 adults each year. The annual incidence rate for meningitis in Europe is estimated to be 1–2 per 100,000 (WHO 2003). The invasive pneumococcal infection is prevalent world-wide but most of the burden in the less developed word, where it accounts over 60 percent of invasive disease worldwide.

2.4.3.d Escherichia coli

The agent

Escherichia coli are Gram-negative, straight rod shaped bacteria cells that are grouped with other related bacteria (that normally live and form part of the intestinal microflora in humans and warm-blooded animals) as 'enteric' bacteria (Thomas 2005). Cases of community acquired bacterial meningitis caused by *E. coli* occur occasionally. They are most common in the neonates and older.

The host

A 27 year review of CABM in a Massachusetts hospital reported that 3% of all infections by G-negative bacilli where community acquired G-negative cocci, other than *H. Influenzae* (Durand, Calderwood et al. 1993). The majority of the affected are elderly or/and neurosurgical patients (Harder, Moller et al. 1999).

Time

There has not been much significant evidence of change in the epidemiology of *E. coli* meningitis amongst adults or neonates over recent time. A small drop in fatality among neonates has been reported, but no reports about adults are available (Holt, Halket et al. 2001).

Place

In Europe, North America and Australia the incidence of community acquired *E. coli* meningitis is low (Bouadma, Schortgen et al. 2006). In parts of Africa and Asia, in the Far East in particular, however, *E. coli* is a more common cause of bacterial meningitis accounting for up to 15% of adult meningitis cases (Chotmongkol and Techoruangwiwat 2000), (O'Dempsey, McArdle et al. 1994).

2.4.3.e Listeria monocytogenes

The agent

Listeria monocytogenes is a Gram-positive rod-shaped bacterium. The invasive infection caused is referred to as listeriosis; and is generally caused by eating food contaminated with the bacteria.

The host

The majority of cases of meningitis caused by *L Monocytogenes* occur in neonates or the elderly, aged 65+, pregnant women and adults with weakened immune systems are also at increased risk of infection (Lavetter, Leedom et al. 1971). The incidence of listeriosis in Europe is not high, around 0.3 cases per year per 100,000, but it is characterised by a high case-fatality rate which can exceed 30% (Goulet and Marchetti 1996; de Valk, Jacquet et al. 2005).

The increase in HIV incidence has been reported to have also resulted in an increase in the incidence of invasive disease due to *L Monocytogenes* in general, and in particular a relatively greater increase in meningitis (Jurado, Farley et al. 1993)

Time

Since the 1990s there has been a fall in the incidence of meningitis due to *L monocytogenes* in Europe, as also a fall in other invasive disease (Tappero, Schuchat et al. 1995). As most infections occur via the oral route, increased food hygiene measures are thought to have contributed to the drop in the incidence. This fall is in contrast to the increased incidence observed in the African countries, in particular in the high HIV prevalence countries (Jurado, Farley et al. 1993).

Place

Meningitis due to *L. monocytogenes* is common world-wide. In Western countries it is one of the most common forms, following Meningococcal and pneumococcal meningitis (Schlech, Ward et al. 1985; Sigurdardottir, Bjornsson et al. 1997).

2.4.3.f Group B streptococcus (GBS)

The agent

Group B Streptococcus (GBS), also known as *Streptococcus agalactiae,* is a Gram positive bacteria, a common coloniser of the gastrointestinal and the urogenital tracts.

GBS is the most common bacterial infection in newborns in the UK, resulting in sepsis, pneumonia and meningitis. It causes around 700 new infections each year, with a case fatality rate of over 10%. Most of the serious disease and fatality from GBS infections is due to meningitis and occurs in the first week of birth (RCOG and LSHTM 2007).

The host

Neonates are at highest risk with incidence around 10/100,000; case fatality rate around 5% (Zangwill, Schuchat et al. 1992; Kyaw, Clarke et al. 2002). Most of the infection occurs in the first weeks after birth and is associated with perinatal infection (Schuchat, Deaver-Robinson et al. 1994). In the UK the prevalence of GBS infection in infants is estimated to be 48 per 10,000, and over half of those infections result in clinical meningitis (Heath, Balfour et al. 2004). Screening strategies for GBS infection of mothers to be have been examined and vary around the developed world (Jafari, Schuchat et al. 1995). A substantial burden of GBS related illness occurs outside the perinatal period, i.e. in pregnant women and infants.

The risk of community-acquired group B streptococcal meningitis in adults increases with increasing age and presence of long-term chronic (Jackson, Hilsdon et al. 1995).

Amongst adults the most common clinical presentation of GBS is sepsis, followed by pneumonia and then meningitis, accounting for around 5% of GBS cases (Jackson, Hilsdon et al. 1995).

Time

The GBS meningitis emerged as a disease in the late 1970s – as a significant cause of neonatal disease but also owing to its rising incidence in adults (Farley, Stephens et al. 1992; Farley, Harvey et al. 1993). In the last decade or so there has been a fall in the incidence of GBS invasive disease amongst infants, coinciding with advanced prevention guidelines in most of the Western countries (Farley, Harvey et al. 1993). However, the disease burden in adults remains substantial and a study in the US reported a significant increase between late 1990s and 2005 (Phares, Lynfield et al. 2008).

Place

Worldwide, colonisation by Group B Streptococcus (GBS) is highly prevalent among pregnant women and amongst the elderly, varying between 4% and 30% (Hickman, Rench et al. 1999; Edwards and Baker 2005). World-wide the most common neonatal meningitis is caused by GBS, and it is also prevalent in older adults (Schwartz, Schuchat et al. 1991). As with other infections, globally, the people at higher risk are those in deprived and marginalized communities (Mayon-White 1985; 1995; Collins, Calderon et al. 1998; Zusman, Baltimore et al. 2006).

2.4.3.g Mycobacterium tuberculosis

The agent

Mycobacterium tuberculosis (*M.tuberculosis*) is a pathogenic aerobic bacteria that stains poorly on Gram stain, and stains better with Ziehl-Neelsen or acid-fast staining. It is the causative agent of tuberculosis (TB), including tuberculous meningitis (TBM) (Jenkins 1994; Plorde 2003).

The host

Only about 10% of infections with *M.tuberculosis* progress to an active disease. Predisposing factors for the development of active TB include malnutrition, alcoholism, substance abuse, diabetes mellitus, corticosteroid use, malignancy, head trauma, and HIV infection (Berenguer, Moreno et al. 1992; Verdon, Chevret et al. 1996). Homeless persons, people in correctional facilities, and residents of long-term care facilities also have a higher risk of developing active TB compared with the general population (Aviglione and Nunn 1997).

Approximately 15-20% of these cases occur in children younger than 15 years. In the developing world, 10-20% of persons who die of TB are children.

In the developed countries rates of the disease are highest in the ethnic minorities and the younger and elderly are at an increased risk of the disease (Stead, Senner et al. 1990; Grange and Yates 1994). Children under 5 are also more likely to develop TBM compared to other forms, including pulmonary TB. Older men also are at a higher risk compared to women of similar ages (Nelson, Schneider et al. 2004).

Time

During the last 2 decades there has been a re-emergence of TB and tubercolous meningitis (TBM) (Nelson, Schneider et al. 2004). The co-epidemic of HIV is thought to be the greatest factor for the recent increase of active TB, along with the social disturbances including, poverty, lack of functioning public health and health service infrastructure leading to large movements of populations as well as emergence of resistant *M.tuberculosis*. In particular there are reports to show that TBM's proportionate increase has been larger than all other forms of TB in recent decades, for example in the 1990s the US saw TBM constituted 6.2% of morbidity attributed to extrapulmonary TB compared to 4.7% in the period before 1990s (CDC 2008).

Place

The incidence of TBM is related to the prevalence of TB in the community, and is still the most common type of chronic CNS infection in developing countries (Karstaedt, Valtchanova et al. 1998; Ramachandran 2007). In many areas of Africa and Asia, the annual incidence of TB infection for all ages is approximately 2% (CDC 2007).

2.4.4 How the disease is transmitted

Generally, the bacteria causing meningitis are transmitted from person to person through exhaled respiratory droplets. The exception is *E. coli* and *L. monocytogenes*, which are transmitted primarily through direct contact via the oral-oral route. Also, GBS is often, and most commonly in neonates, transmitted through direct skin contact.

Most of these bacteria usually inhabit the nose, throat and respiratory tracts of warm blooded animals, including humans, with the exception of *N. meningitidis* which only infects humans and it is not know to infect animals. The bacteria are commonly carried in the pharynx (so called asymptomatic nasopharyngeal carriage) which sometimes, for reasons not fully understood, may invade the bloodstream and reach the brain. In this way, these bacteria can cause much illness, including infections of middle-ear, lungs (pneumonia), sepsis and meningitis (Trotter and Greenwood 2007).

Factors that influence the spread of bacteria have been described to be behavioural frequent and close person-to-person contact with an infected person (e.g. kissing, sneezing and coughing.) Also included within this is demographic; movement of populations such as social disruptions or pilgrim movements, environmental; drought, economic; poor nutrition and overcrowding leading to reduced immunity, epidemiologic; agent and host interactions, and social; smoking, overcrowding, living

in close quarters or dormitories (as do military recruits and students) (Cartwright 1994).

2.4.5 Carriage and invasive disease

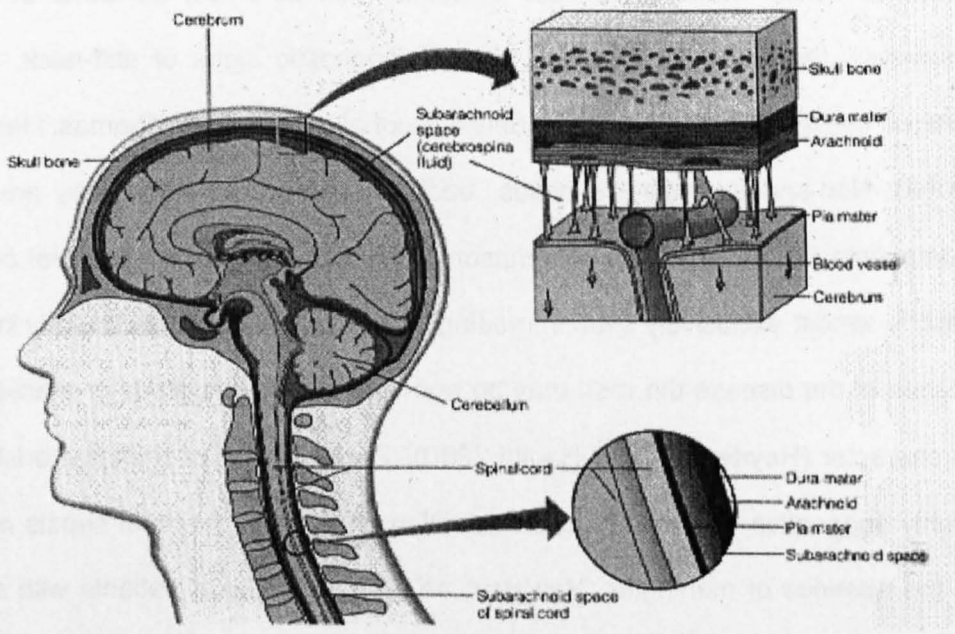
The 3 main pathogens responsible for causing CABM *(N.meningitidis, S. pneumonia and HiB)* are normally carried on the back of the throat (nasopharynx) of healthy people. It is estimated that between 10 to 25% of the population carry *HiB*, *N.meningitidis* whilst pneumococci up to 40%, at any given time, the carriage rate may be much higher in epidemic situations and day care centres (Stephenson, Doern et al. 1985; Crook, Brueggeman et al. 2004). The rates of carriage vary by population groups, seasonality and outbreak occurrence; and in all of these instances the carriage transmission follows a trend as in disease transmission. As such, the carriage is higher in young children and adolescents, in populations living in overcrowded settlements, in winter times and in times of outbreaks or epidemics (Cartwright, Stuart et al. 1987).

The pathway of the transmission of the pathogens from one individual to another can result in colonisation (carriage), disease or it can be just transient. As per disease acquisition, the risk factors for carriage include: smoking, severe overcrowding, and age-group (Cartwright 1994).

2.5 Pathology, clinical presentation and management of bacterial meningitis

2.5.1 Recognition of meningitis

Figure 2.5 - The central nervous system



Early recognition of suspected meningitis cases followed by prompt institution of therapy is central to improving patient outcomes. The clinical features of meningitis in its early stages are often non-specific and a high index of suspicion is needed in order for the clinician to identify a case of meningitis from the many patients with febrile illnesses that present to the emergency departments. It is supposed that in some patients, the severity of the illness may be masked by the prior administration of antibiotics.

Presenting symptoms vary with age at onset and, as per causation, the clinical presentation can be grouped into the newborns (from birth to one month of age), infants (2 months to 2 years), children over 2 years of age and young teenagers and adults. The common symptoms and signs, across all age-groups include fever,

headache, neck stiffness, photophobia, nausea and vomiting, impaired or fluctuating mental status, focal neurology and seizures (Durand, Calderwood et al. 1993).

Amongst adults a headache is the most common symptom of meningitis followed by neck stiffness, both present in around 80% of cases (however neck sitffenes sometimes less, particualry in the elderly, see below), and focal neurology and seizures which affect up to 15% of adults (van de Beek, de Gans et al. 2004). However, the recognised typical triad of diagnostic signs of stiff-neck, fever and altered mental status is present in only 44% of all adult cases (Thomas, Hasbun et al. 2002). Non-specific muscles aches, back pain and cold extremities are common complaints of adult patients (Thompson, Ninis et al. 2006). A petechial or purpuric rash is almost exclusively seen in meningococcal disease, but particularly in the early stages of the disease the rash may be non-specific erythematous or maculo-papular in character (Heyderman and Habibi 2000). The presence of a characteristic rash is highly suggestive of meningococcal infection, and meningococcal sepsis may occur in the absence of meningitis. However, as many as 50% of patients with confirmed meningococcal meningitis may not have a rash at presentation.

This is difficult to be made with precision through diagnosis in clinical examination alone (Carpenter and Petersdorf 1962; Durand, Calderwood et al. 1993; Attia, Hatala et al. 1999). The absence of all 3 classical features of meningitis, i.e. fever, headache and altered mental status, essentially excludes the diagnosis. Meningitis is particularly difficult to diagnose in the elderly because of high prevalence of underlying illnesses and the less specific presentation. Neck stiffness has been reported to be present in as few as 35% of patients older than 60 years (Puxty, Fox et al. 1983) and a depressed level of consciousness may occur in many forms of severe infection in this age group (Behrman, Meyers et al. 1989; Choi 2001) { Miller, 1997 60 /id} (Gorse, Thrupp et al. 1984). A high index of suspicion is therefore needed across all age groups, not only children and teenagers (Table 2.1). It is

recommended that the diagnosis of meningitis should be carefully considered in any patient with headache, confusion, irritability or lethargy, with or without a fever.

Table 2.1 - Symptoms and signs of meningitis in adult patients adapted from Durand et al. and Attia et al.

Signs and symptoms	Percentage present
Fever	95%
Neck stiffness	88%
Altered level of consciousness	79%
Headache and/or photophobia	50%
Seizures or focal neurology	23%
Rash	11%

2.5.2 Initial assessment and management

Meningitis is a disease with a sudden onset and a rapid progress, therefore immediate intervention is required if a diagnosis of meningitis is suspected. In 2005 the British Infection Society (BIS), to assist clinicians in diagnosing and treatment of meningitis, developed a management algorithm for the management of adults based on previously published guidelines (www.britishinfectionsociety.org or www.meningitis.org) (Begg, Cartwright et al. 1999). These guidelines constitute the core benchmarking document for the review of clinical management of CABM and MS and in the formulation of the standards against which the clinical hospital management are reviewed (Chapter 6). A copy of the standards and indicators developed for use in the review of clinical management is presented in Appendix 3.

Initial Assessment

A number of clinical signs / symptoms and laboratory tests are recommended to be assessed and documented in the initial assessment of a patient with meningitis/septicaemia. Below are some of the key ones, grouped as per clinical

relevance which has formed the basis of the data-collection instrument for the review of clinical management, presented in Chapter 6.

- Assessment of the patient's airway, breathing (respiratory rate and oxygen saturation) and circulatory status (pulse, urine output, capillary refill time).
- Assessment of the warning signs of severe disease (Table 2.2), including the level of consciousness.
- A number of laboratory examinations, including a full blood count, blood glucose, urea and electrolytes, liver function tests, C-reactive protein, a clotting profile are needed (Corless, Guiver et al. 2001; Jordens, Williams et al. 2002)
- In presence of the warning signs of severe disease it is recommended to seek assistance from the critical care team.

There are a few issues that have been debatable and controversial in the recent years in the management of CABM and MS. I will review these here in context of my research.

2.5.2.a Rationale for diagnostic lumbar puncture

The approach to the diagnosis of bacterial meningitis by lumbar puncture (LP) has markedly changed over the last 10-15 years (Ramsay, Kaczmarski et al. 1997). It has been debated whether, now that we have potent antibiotics, a LP will be beneficial to inform the management of patients. There is a fear amongst clinicians that a LP is associated with unacceptable hazards in meningitis, primarily cerebral herniation. There are, however, specific and well-accepted contraindications to LP in patients with meningitis (see Table 2.2) and it is essential that these are followed carefully. Otherwise, a LP can be performed safely in the absence of contraindications and provided that it can be undertaken within 30 minutes of initial assessment, does not introduce a significant delay in treatment.

LP provides opportunity for confirmation of the diagnosis, bacteriological culture of CSF may yield the aetiology and antibiotic sensitivities, these being important prognostic information. There are also concerns that performing a LP delays the administration of antibiotics. These indicators have been explicitly addressed in the review of hospital management, Chapter 6.

2.5.2.b Recognition of raised intracranial pressure

Evidence of raised intracranial pressure (ICP) in bacterial meningitis most commonly manifests itself as a fluctuating or deteriorating level of consciousness, or prolonged seizures. These can be confused with the features of cerebral hypoperfusion in the absence of meningeal inflammation with those of raised intracranial pressure in patients with meningitis. Appropriate identification of raised intracranial pressure is key to the indication (or contra-indication) of LP, because of the potential risk of cerebral herniation, discussed below.

Table 2.2 - Signs of raised intracranial pressure (ICP)

Signs of raised intracranial pressure
Marked depression of conscious level: GCS<13 or a fall in GCS >2
Focal neurological signs e.g. 6^{th} or 3^{rd} cranial nerve palsies, hemiparesis
Persistent seizures
Bradycardia and hypertension (Cushing reflex)
Papilloedema (rare in meningitis)

Table 2.3 - Signs of shock and respiratory failure

Signs of shock and respiratory failure
Poor peripheral perfusion
Capillary refill time >4 seconds
Oliguria (urine output <20mL/hour)
Systolic BP <90mmHg
Respiratory rate <4 or >30 breaths per minute
Pulse rate <40 or >140
Acidosis: pH <7.3 or Base Excess worse than -5
White blood cell count <4.0 x 10^9/L

2.5.2.c Rationale for diagnostic computerised tomography before LP

To address the suspicion of raised intracranial pressure (discussed above) it is a common practice to arrange a CT brain scan prior to undertaking a LP in patients with suspected meningitis. This approach is poorly supported by available evidence. Clinically significant raised ICP cannot be ruled out by brain CT and therefore a normal scan can be falsely reassuring (Durand, Calderwood et al. 1993; Hasbun, Abrahams et al. 2001).

Meningitis patients presenting with clinical signs of raised ICP are in the minority and they should not undergo LP regardless of the CT findings. Transporting patients to a CT scanner before they have been adequately stabilised is unsafe and may result in sudden deterioration in an uncontrolled environment.

It is argued that the inevitable delay in undertaking the CT scan requires that empirical antibiotics are given while awaiting the procedure, therefore impairing the diagnostic yield from a subsequent LP, as discussed above. Brain imaging is

considered useful in the investigation of the immunocompromised with suspected cerebral infection and may define a dural defect, in adult patients with otitis media or mastoiditis. However, in the context of community acquired meningitis this approach infrequently identifies conditions requiring neurosurgical intervention (Heyderman, Robb et al. 1992; Durand, Calderwood et al. 1993; Hasbun, Abrahams et al. 2001).

A recent prospective study of adults with suspected meningitis that examined clinical characteristics before CT of the head could be used to identify patients who were unlikely to have abnormalities on CT, concluded that clinical features can be used to identify those who are unlikely to have abnormal findings on CT of the head. Absence of an abnormal level of consciousness, neurological palsy, papilloedema, and abnormal language (e.g. aphasia), yielded a negative predictive value of 97 percent (Hasbun, Abrahams et al. 2001).

2.5.2.d The effect of clinical management in the outcome of meningitis and MS

Much resource is used in developing clinical guidelines, however little is known about their impact in the outcome of the respective conditions. With regard to the management of CABM and MS much emphasis is put on the rapid assessment and management of the suspected cases.

A recent study in meningitis in children and teenagers raised doubts about the benefit of early antibiotic treatment of these conditions (Harnden, Ninis et al. 2006). Also, not much is known on the effect of recommendations that seriously ill patients should be reviewed by a consultant within a set time. I will be examining the association of key clinical management indicators with the outcome of CABM and MS in the last chapter of the results of my research, Chapter 8.

2.5.3 Treatment

2.5.3.a Antibiotics

Antibiotics are the mainstay of treatment and have dramatically reduced the very high morbidity and mortality of meningitis seen in the pre-antibiotic era (Table 2.4).

Earlier in this chapter I briefly presented the historical developments in antibiotic therapy, with sulfonamides, penicillin being in use since the early 1940s and a bit later chloramphenicol. These treatments resulted in significantly reduced morality from meningitis. However, it is only in the last 2 decades or so that mortality fell to around 5 % for HiB meningitis and around 10% for meningococcal meningitis. On the other hand, mortality from pneumococcal meningitis has remained at over 20 percent (Dowling, Sweet et al. 1949; Whitney, Farley et al. 2003).

Deciding on the effective antibiotic treatment of bacterial meningitis depends upon local epidemiology, e.g. the distribution of causative organism across age groups the prevalence of antibiotic resistance. Nonetheless, the third generation cephalosporins are generally used as first drug of choice as they are effective in most cases.

Table 2.4 - Recommended antibiotic therapy for CABM and MS in adults

Organism	***Antibiotic (total daily dose)***
Unknown (suspected diagnosis)[a]	Cefotaxime (8–12 g) or ceftriaxone (4 g) add ampicillin (12 g) in patients >55 years
Streptococcus pneumoniae	
≤0.1 μg/mL	Benzyl Penicillin G (14.4g)
0.1–1.0 μg/mL	Cefotaxime (8–12 g) or ceftriaxone (4 g)
≥1.0 μg/mL	Cefotaxime (8–12 g) or ceftriaxone (4 g) plus Vancomycin (2 g) with or without rifampicin (600-1200mg)
Listeria monocytogenes	Ampicillin (12 g) plus an aminoglycoside: gentamicin, tobramycin (3–5 mg/kg)
Neisseria meningitidis	Benzyl penicillin G (14.4g) or ampicillin (12 g)
Haemophilus influenzae	Cefotaxime (8–12 g) or ceftriaxone (4 g)
Enterobacteriaceae (gram-negative bacilli)	Cefotaxime (8–12 g) or ceftriaxone (4 g)

Except where the patient is well and the diagnosis very uncertain, antibiotics are recommended to be administered empirically, awaiting and depending on the result of a LP. Based on evolving antibiotic resistance and good pharmacological characteristics, the 3rd generation cephalosporins, cefotaxime and ceftriaxone are now the common practice in most industrialised countries, eventhough for MS benzyl penicillin is the recommended first line agent for empirical therapy. *Listeria monocytogenes* is not susceptible to these agents and an amidopenicillin (ampicillin or amoxicillin) is recommended to be given in addition to a 3rd generation cephalosporin in patients older than 55 years, i.e. due to the increased proportionate risk of *Listeria* being a causative agent. Antibiotic resistance has become an important issue in the treatment of meningitis.

It is recommended that patients suspected of having a highly penicillin resistant organism (indications include: recent travel to areas with high levels of penicillin resistant pneumococci such as Southern Africa, Spain and the USA, some of the Eastern European countries) are administered vancomycin together with rifampicin in addition to a cephalosporin. Generally, appropriate antibiotics have a quick effect in cerebrospinal fluid (CSF), sterilising it within 24 - 48 hours after the initiation of therapy, but it is recommended that treatment should continue intravenously for at least 7 days, and for organisms other than *Neisseria meningitides,* usually up to 14 days.

2.5.3.b The use of dexamethasone in adult meningitis

The cerebral damage that occurs in bacterial meningitis is largely due to a host mediated inflammatory response (Pfister and Scheld 1997; Nau and Eiffert 2002). This process is triggered by the release of bacterial toxins and is exacerbated by antibiotic treatment. Several well conducted controlled trials have demonstrated improvements in morbidity (deafness or neurological deficit) but not mortality with adjunctive dexamethasone therapy for suspected bacterial meningitis in children (van

de Beek, de Gans et al. 2003), (Duke, Curtis et al. 2003). Until recently, in contrast to paediatric practice, there has been little evidence to support the routine use of steroid therapy in the management of adult patients with meningitis. A large multicentre, double-blind, randomized and placebo controlled trial of 301 patients (de Gans and van de Beek 2002) has shown a significant benefit in outcome (mortality and morbidity) with the administration of 10mg dexamethasone together with or within 20 minutes of the first dose of antibiotic and given every 6 hours for 4 days. Importantly, there was no increase in adverse events attributable to dexamethasone therapy in the treatment group compared to the control group.

A systematic review states that "dexamethasone should be given to all adults with bacterial meningitis and should be initiated before or with the first dose of antibiotics" (van de Beek, de Gans et al. 2003). In light of this study it is now recommended an adjunctive dexamethasone in all adult patients presenting with suspected bacterial meningitis in the absence of known contra-indications to steroid therapy. Should an alternative diagnosis be made subsequently then the steroids can be stopped. The benefit of steroid therapy underlines the importance of diagnostic lumbar puncture in order to confirm the presumptive diagnosis (Quagliarello 2004).

When I designed and undertook the review into clinical management there was no recommendation for use of dexamethasone in treatment of adults with meningitis therefore I have not examined this practice in my research.

2.5.4 Follow-up and long-term complications

The outcome for the individual patient with bacterial meningitis is influenced by many factors including age, time before effective antibiotic therapy, aetiology and the intensity of the host inflammatory response. This is an area that attracts little attention particularly in adult practice.

Neurological deafness is the commonest complication associated with bacterial meningitis but over 30% of individuals will have some form of long-term complication including behavioural problems, cognitive impairment, seizures and focal neurological deficits (Erickson and De Wals 1998; Erickson, De Wals et al. 2001). Therefore, it is recommended that all patients undergo audiological assessment before discharge and in convalescence.

2.5.5 Public health management of CABM and MS

Clinicians are required to notify all suspected cases of meningitis to the local Consultant in Communicable Disease Control (CCDC) for contact tracing and provision of prophylaxis (in cases of meningococcal meningitis), within the first 12 hours of diagnosis. The recommendation is that close contacts of the patient (defined as household, kissing, or other close contact) are treated with a prophylactic antibiotic, rifampicin, cirprofloxacin or ceftriaxone. The aim of this prophylaxis is to reduce the carriage for direct reduction of the risk of the disease to close contacts. All index cases of MD should also receive chemoprophylaxis in order to clear the throat carriage of *N. Meningitidis (Public Health Laboratory Service, Public Health Medicine Environmental Group et al. 2002)*. This will be described in more detail further in this chapter.

2.6 Reporting of cases of CABM and MS

Cases of the suspected or confirmed bacterial meningitis and MS in England and Wales are reported through 2 major routine sources: the clinical notifications and the laboratory reports.

All forms of bacterial meningitis examined in this thesis are notifiable diseases under the Public Health (Infectious Disease) Regulations 1988. Below I will give a very brief introduction to the 2 major routine reporting systems of forms of CABM and MS. Table 2.5 presents the main characteristics of routine data sources available in England and Wales and used in my research. A detailed description of the routine data sources used in my research is presented in the following chapter, 'Data and Methods.'

2.6.1 Clinical notifications

The Department of Health (DH) guidance on Notification of Infectious Diseases states: "Section 11(1) of the Public Health (Control of Disease) Act 1984 provides that if a registered medical practitioner becomes aware, or suspects, that a patient whom he is attending is suffering from a notifiable disease or food poisoning, he shall forthwith send to the relevant local authority a certificate with details of the case. This requirement applies to any registered medical practitioner in England (or Wales). Under section 11(4), it is a criminal offence to fail to comply with an obligation imposed by section 11(1). (DH 2006). The available data on notifications of infectious diseases (NOID) include listing for: date of birth; sex; suspected diagnosis based on ICD10 codes; residential address; reporting clinician. These notifications are collected, collated and maintained by the Office for National Statistics (ONS), and are available usually with a year time lag.

Table 2.5 - Routinely available data sources used in this research

Data Source	Description	Relevant results chapter
Population data	Usually based on the census of the population in the UK. Undertaken once ever ten years. They present mid-year population estimates, derived from the latest census.	Chapter 4
Clinical notifications	All clinicians in E&W have a duty to report cases of a list of infectious diseases. The data includes: demographics, address, suspected / confirmed causative agent / disease.	Chapter 4; Chapter 5
Hospital Episode Statistics	A minimum data set is kept that includes information on all inpatients and outpatient. Information comprises of: demographics, clinical information including: ICD 10 codes for diagnosis, treatment, ward, consultant's specialty, etc.	Chapter 5
Laboratory data	The Centre for Infection of the HPA collects the data on laboratory confirmations (culture, titre, PCR and other test) of infectious diseases. Data comes from a number of sources, including: NHS/HPA laboratory reports, samples sent directly to CfI from GP practices, reference laboratories, etc.	Chapter 4; Chapter 5

2.6.2 Laboratory reporting

Laboratory confirmation of samples tested for certain pathogens', including the bacterial causes of meningitis and MS, across the NHS laboratories in England and Wales are reported to a designated part within the Centre for Infections of the Health Protection Agency (HPA).

The reporting is done as part of two systems:

- Routine lab reports and
- Enhanced laboratory surveillance – for some of the microorganism additional data about cases reported under routine surveillance is collected. This information may be sought from the reporter, the case, the laboratory or from another surveillance data set. Enhanced surveillance

for *S.pneumoniae* and *N. meningitidis* for example contains information on the age, sex, address, vaccination status; this information is collected from various sources and is then collated into one database.

2.6.3 Surveillance of CABM and MS in England and Wales

Data on the epidemiology of CABM and MS in England and Wales usually comes from the routine surveillance systems. Surveillance is often defined briefly as data for action. The full definitions reflect exactly that, eg the WHO definition "The process of systematic collection, orderly consolidation and evaluation of pertinent data with prompt dissemination of the results to those who need to know, particularly those who are in a position to take action." (WHO 1999).

Surveillance data have been useful in following trends and documenting the effect of the new protein-conjugate vaccines against *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC) that were introduced in the 1990s (Ramsay, McVernon et al. 2003),(Ramsay, Andrews et al. 2003).

2.6.3.a The usefulness of routine data

There are a number of advantages and opportunities in using routinely collected data for examining the epidemiology of infectious diseases in general and CABM and MS, in particular (Doyle, Glynn et al. 2002). Some of these are:

Resource efficiency

Routine surveillance data is available at low cost to researchers / health professionals, providing an opportunity for not only yielding useful results but also developing and improving data management and interpretations skills.

Comprehensiveness and completeness

Routinely collected data sources, and in particular data on CABM and MS, usually contain sufficient information for following trends from the whole population of England and Wales (McCormick 1993). As described above these data are collated and published nationally, by the ONS, and are therefore readily available for research purposes.

Geographical trends

Routinely collected data for CABM and MS are based on standard reporting forms, enabling, generally, a meaningful comparisons between geographical areas, health care services or regional figures (Thacker, Redmond et al. 1986). Provided there are no major differences in the definitions of a case, comparison can be made across national figures, e.g. between different EU countries, as well. I have examined the regional differences in the incidence rates of CABM and MS in England and Wales, presented in Chapter 4.

Time-trends

Surveillance data have been shown to be useful for trend analysis of the disease over time; as discussed above for HiB and Men C, for instance. Also population data for England and Wales is available to make time trend comparisons, as population censuses are carried out every 10 year, following similar methodologies and data collection formats. I have applied time trends analysis in examinig the epdiemioogy of CABM and MS in England and Wales, and these will be presented in Chapter 4.

2.6.4 Limitations of routine data sources

Despite the usefulness of routine data, their shortcomings and limitations are well acknowledged (MacLehose, McKee et al. 2002). Common problems with routine data are time-lag, lack of completeness of data and lack of representativeness. Probably the biggest problem is that only a proportion of the cases that should be reported are actually reported.

It is widely accepted that infectious diseases, including CABM and MS, are commonly underreported (Reintjes, Termorshuizen et al. 1999). Population based surveys and active surveillance systems, the ideal methods for estimating prevalence and incidence of disease, are resource intensive, whereas passive surveillance systems are not. To obtain more realistic estimates of prevalence, methods such as capture-recapture (Smith, Stuart et al. 1998) have been used effectively for both chronic disease and infectious disease epidemiology (Hook and Regal 1995; Faustini, Fano et al. 2000). I applied this method, which is described in detail in Chapter 3 (Data and Methods) and the results are presented in Chapter 5.

2.6.5 International surveillance of CABM and MS

A number of European surveillance networks have been developed between the countries of the EU over recent years, including: influenza networks, EuroHIV and EuroTB, food and waterborne and vectorborne diseases.

The ECDC's programme on vaccine-preventable diseases (VPD) was set up in 2006 and covers vaccination issues in general, including surveillance of invasive bacterial infections, which are common causes of CABM,: *Haemophilus influenzae type B* (HiB), *Neisseria meningitidis*, and *Streptococcus pneumoniae* (Pierluigi Lopalco 2008). The

specific priorities with regard to invasive bacterial diseases, which cause most of the CABM and MS, for ECDC are:

- Harmonising and strengthening surveillance of *N. meningitidis*, *H. influenzae* and *S. pneumoniae* in the Member States;
- Improving laboratory capacities;
- Standardising laboratory surveillance methodologies in the Member States;

These efforts not only will improve surveillance and public health capacities in the member states but also will make the systems comparable and strengthen our evidence for action (Lopalco 2008).

2.7 Prevention of CABM and MS

Prevention of CABM and MS is an important factor in the overall control of the disease. There are 2 main forms of public health intervention in prevention, namely prophylaxis with antibiotics and vaccination.

The public health policies and practices on managing cases of CABM and MS vary across European countries. The public health management, which normally includes prophylaxis and / or vaccination to close contacts, is aimed at 1) reducing the risk of transmission of *N meningitidis* from the index case; or 2) reducing the risk of infection, respectively. A European survey revealed differences in definitions of close contacts and prophylactic regimens between countries and recommended the development of guidance for best practice in priority areas, based on evidence or consensus (Hoek, Hanquet et al. 2008).

2.7.1 Prophylaxis

In cases of meningococcal meningitis, and to some extent of HiB meningitis, prophylactic treatment of close relatives with antibiotics (e.g. rifampicin, ciprofloxacin or ceftriaxone) reduces the carriage and may reduce the risk of further cases (Fraser, Gafter-Gvili et al. 2006). The index case is also treated with a prophylactic antibiotic, usually rifampicin before discharge from hospital, or if the treatment course included benzyl penicillin it is effective in reducing nasopharyngeal carriage (Fraser, Gafter-Gvili et al. 2005). Nonetheless, because only about 2% of meningitis cases are linked to an index case, chemo-prophylaxis to close contacts of an index case has probably a limited effect on the overall epidemiology of meningitis.

2.7.2 Vaccination

Vaccination is an important and significant preventative measure for CABM and MS. Different vaccines are available for the most common causes of CABM, and the most commonly used include: vaccines against *N. meningitidis* (some groups); *S. pneumoniae*; *H. influenzae type B*; the BCG (against TB).

2.7.2.a Meningococcal vaccination

Several meningococcal vaccines are available and in use. Including polysaccharides A, C, W135; and the Conjugate C vaccine.

Several vaccines are available to prevent the disease. Polysaccharide vaccines, which have been available for over 30 years, exist against serogroups A, C, Y, W135 in various combinations. A monovalent conjugate vaccine against serogroup C has recently been licensed in developed countries for use in children and adolescents. This vaccine is immunogenic also for children under 2 years of age in contrast to polysaccharide vaccines, which are not. All these vaccines have been proven to be safe and effective with infrequent and mild side effects.

The serogroup C caused high number of deaths in young children and teenagers. The high mortality, anxiety and public health impact, together with the resulting media pressure, are argued to have contributed to the decision to introduce Men C vaccination into routine childhood immunisation schedule in 1999. This vaccination programme has resulted in more than 90% reduction rate of Men C infections (Ramsay, Andrews et al. 2001; Ramsay, Andrews et al. 2003) and in April 2008 the news headlines where – "*No deaths from Men C*" (news.bbc.co.uk/2/hi/health/7354722.stm). However, serogroup B continues to be a high cause of disease in children in UK.

With regard to a vaccine for serogroup B there has been some progress, but we still do not have an effective vaccine in use. Current *N. Meningitidis serogroup B* vaccines

based on outer-membrane proteins do not provide protection for infants or long-lasting immunity in adults. Therefore alternative vaccinations strategies have been explored. Below are summarised research attempts to use:

- mucosal immunisation, rather then humoral immunisation, and
- immunisation with *Neisseria lactamica* (a non-pathogenic type of *Neisseria* bacteria), rather then *N. meningitidis*, for generating effective immunity against Men B disease.

As natural carriage of *N. meningitidis* and related bacteria leads to the development of protective immunity both at the mucosal surface and in the circulation (Horton, Stuart et al. 2005), vaccine strategies that mimic this natural immunization process would better-optimize vaccine-induced protective immunity have been proposed. Thus, mucosal immunization before a systemic booster vaccination could provide the solution and reduce the necessity for multiple injections to achieve immunity (Heyderman, Davenport et al. 2006).

Other developments in meningococcal vaccine stretch towards research in the use of other bacteria within the *Neisseria* family in generating protection against the pathogenic *N. meningitidis*. Recently, studies have found that immunisation with killed *N. lactamica* whole cells and outer membrane proteins offers protection and cross reactivity with *N. meningitides*. These findings support the idea that successive colonisations with *N. lactamica* (in childhood) enhance the anti-meningococcal immune response (Oliver, Reddin et al. 2002; Sanchez, Troncoso et al. 2002), (Troncoso, Sanchez et al. 2002); confirming, thus, the idea for the potential of *N. lactamica* based vaccines, and providing evidence for commencing vaccine trials (Gorringe, Halliwell et al. 2005; Davenport, Groves et al. 2008).

2.7.2.b Hib vaccination

Hib Conjugate vaccine has been used in Western countries for over 15 years, where it has resulted in dramatic decrease of incidence and mortality almost an elimination of HiB disease (Rushdy, Ramsay et al. 1999; Ladhani, Slack et al. 2008). But is still not widely used in the developing world where is most needed (Adegbola, Usen et al. 1999). This is despite evidence of its great success in developing countries, such as The Gambia, in West Africa, where Hib meningitis and severe pneumonia in young children have virtually been eliminated following implementation of routine infant vaccination against Hib. In Malawi and Gambia a large decline in HiB incidence since introduction of Hib Conjugate vaccine, from around 60 to about 5 in 100,000 per year (Adegbola, Secka et al. 2005; Daza, Banda et al. 2006).

2.7.2.c Pneumococcal vaccine

A type of *Streptococcus pneumoniae* vaccine is already in routine use in most of the Western countries, and that the conjugate vaccine is now used in children's immunisaiton programmes, e.g. in UK-Pneumovar; whilst a polysaccharide vaccine is generally used among at risk adults.

Clinical trials conducted in South Africa and The Gambia has shown that a 9-valent vaccine is extremely effective in preventing pneumococcal disease in the less developed countries/populations. If used routinely, a pneumococcal conjugate vaccine could prevent hundreds of thousands of child deaths each year and contribute to achieving the United Nations 'Millennium Development Goal' to decrease childhood deaths by two-thirds by 2015. The Global Alliance for Vaccines and Immunization (GAVI) works towards making these vaccines available for the developing countries. Some if the initial effect of the PCV in the population (in countries wehre introduced as a programme) have been: shift of the disease towards adults, change of serotypes (ie increase in non-

vaccine type disease), heard immunity and reduction in anitbiotic resistance strains (Hsu, Shutt et al. 2009; Kaye, Malkani et al. 2008).

2.7.2.d Bacillus Calmette-Guerin vaccine

The Bacillus Calmette-Guerin (BCG) vaccine is an attenuated strain of the M. tuberculosis that is used to prevent tuberculosis. The vaccine is used in national programmes of immunisation in many countries around the world, and where the incidence of TB is high.

In the developed countries, including the UK, where the TB incidence is low, it is usually used for vaccination of high-risk groups, such as babies born of parents with origin from high risk countries. There has been debate around the effectiveness of the BCG vaccine (Murtagh 1980), but a recent meta-analysis provided evidence that vaccination is cost-effective at preventing tuberculous and miliary meningitis rather then pulmonary, particularly so in southeast Asia, Africa, and the western Pacific region, where tuberculosis infection rates and BCG coverage are highest (Trunz, Fine et al. 2006)

2.8 A summary of the background

Bacterial meningitis and meningococcal septicaemia are important causes of preventable morbidity and mortality in the UK and worldwide.

Most of the information on the epidemiology, clinical picture and disease outcomes comes from studies on paediatric or teenagers population, which have different individual characteristics from adult population. Moreover, efforts to improve management have mainly concentrated on paediatric care. However mortality amongst young adults remains higher than amongst children and recent studies suggests deficiencies in health care delivery to adult cases. The introduction of the conjugate vaccination programmes has significantly changed the epidemiology of CABM and MS in children, and there are data to show a level of herd immunity, which might have affected the disease in adults as well. Under-reporting of infectious diseases is well-acknowledged and determining its level for meningitis would be useful for planning control and prevention programmes.

Chapter Three

Data and Methods

Chapter Three – Table of content

3.1 Introduction to data and methods

To address the objectives of my research (see Chapter 1) I have used different methodologies and different data. These can broadly be classified as:

1) Data and methods for the Epidemiological research; and

2) Data and methods for the Clinical management research.

Therefore, in this Chapter I will follow this broad classification, to describe the different data and methods as follows.

Firstly, I will describe the case definitions I use, which are common to both aspects of my research (epidemiology and clinical management). I will then describe the methodological approaches specific to each aspect. Within these 2 broad categories I will describe the study design, data, data collection and management. The last part of the chapter describes the statistical methods used.

3.2 Case definition

Cases included in this research were defined as: any adult (age 16 years or older) with CABM and MS diagnosed between 1991 and 2002 in England and Wales. Below I will give the details of each main aspects of the case definition, which will apply to both incidence and deaths.

3.2.1 Causative organism

The following causative organisms were included in the definition of the CABM:

Neisseria meningitidis (*N. meningitidis*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*), *Listeria monocytogenes* (*L. monocytogenes*),

Mycobacterium tuberculosis (*M. tuberculosis*), *Group B Streptococcus* (*GBS*) and *Escherichia coli* (*E. coli*).

The rationale for including the above listed causative organisms as CABM was based on the relevant literature showing the most common community acquired causative organisms of bacterial meningitis. This was complemented with advice from experts on the subject (K. Cartwright, R. George and J. Stuart) to include causative organisms that, based on literature review are likely to be community acquired, and for which there are at least 50 reports each during the ten year period (1990 to 2000).

3.2.2 Time

Overall the study included cases of CABM and MS in the years 1991 to 2002. Different parts of the study used slightly different time boundaries for cases, but all are within the period mentioned above. Table 3.1 sets out the time period relevant to each part of the research. The death data based on notifications to the ONS were available by different causative organisms only from 1993.

Table 3.1 - Time period relevant to research objectives.

Research objective	Date period	Chapter with results
Current epidemiology	1 January 1991 to 31 December 2002	Chapter 4
Improving estimates of disease measure: capture-recapture analysis	Incidence: 1 April 1996 to 31 December 1999	Chapter 5
	Mortality: 1 April 1996 to 31 March 2000	
Review of clinical management	1 January 2001 to 31 December 2002	Chapter 6
Association of clinical management with outcome	1 January 2001 to 31 December 2002	Chapter 7

3.2.3 Place

Cases included in this research are from England and Wales. Within the examination of the epidemiology (Chapter 4) there is a part which examines the trend of the lumbar punctures (LP), and uses data from the NHS Administrative Region of the South West (SW region), only. The capture-recapture analysis (Chapter 5) uses data from England, only. A part of this analysis, the verification of the analysis uses data from the SW region, only.

3.3 The epidemiological research

This part of the research addressed two of the main objectives of this thesis, objectives 1 and 2 (results presented in Chapters 4 and 5).

3.3.1 Examination of the current epidemiology

I analysed the available routinely collected data on CABM and MS on adults in England and Wales, for the period 1991 – 2002 using appropriate statistical regression methods, detailed below. I performed a thorough analysis of the epidemiology of CABM and MS with particular focus on the distribution of disease by years and the causative bacteria among age-groups, gender. The population data from ONS (mid year estimates) for each corresponding year was used to calculate incidence and mortality rates.

3.3.2 Improving estimates – a capture-recapture analysis

I undertook a capture-recapture analysis to obtain a better estimate of the 'true' burden (incidence and mortality) of CABM, using 2 data sources, than available from single sources owing to under-reporting. Pneumococcal meningitis was used as an indicator for other causative forms of CABM, as well. The rationale behind this was that:

- A specific case-definition provides more reliable surveillance data than a loose definition, so if all forms of CABM had been included the quality of the data would have been lower;
- Pneumococcal meningitis is one of the two most common forms of CABM
- Clinically pneumococcal meningitis is one of the distinctly defined forms of CABM
- A similar study into meningococcal meningitis was being undertaken by others at the time. Therefore by using pneumococcal meningitis I was able to make a useful

contribution to the literature, and have a valid comparison to the available estimates for the disease burden.

3.4 Data and research methods for the epidemiology research

Here I describe the data sources used for the all of the epidemiological research, including examination of the current epidemiology and the capture-recapture analysis.

3.4.1 Incidence data

These were derived from: Laboratory reports (including routine, enhanced or reconciled surveillance), HES and ONS.

a) Health Protection Agency (previously Public Health Laboratory Service)[2]

Surveillance is described as the ongoing systematic collection, analysis, interpretation, and dissemination of data for public health action (Buehler 1998.). In England and Wales the surveillance for CABM and MS is based on laboratory reports and clinicians' notifications.

- **Laboratory reports**

All samples taken for laboratory investigations upon suspected diagnoses of CABM and MS are tested by the local NHS and HPA (formerly PHLS) laboratories. Results from these tests are forwarded to the Center for Infection (CfI) (formerly CDSC), in Colindale London. For some causative organisms of particular public health relevance, such are *N.Meningitidis, S.Pneumoniae, HiB*, there are enhanced surveillance systems in place, and reference laboratory units. The laboratory data that are produced by and managed at the Reference Unit laboratories is referred to as Reconciled Laboratory Reports (RLR). This usually means that the surveillance is more sensitive (because of enhanced

[2] This organisation as from April 2003 has become part of the Health Protection Agency (HPA).

reporting and more advanced testing methods) and contains additional information, as compared to the routine laboratory reports. I will briefly describe the laboratory surveillance for the most common causative organisms of CABM in England and Wales.

Neisseria meningitidis

All requests, from the local clinicians or local laboratories, for laboratory testing of blood and CSF samples on meningococcal infections are sent to the Meningococcal Reference Unit (MenRU) in Manchester. There testing is performed for culture and polymerase chain reaction (PCR) of N.meningitidis and, amongst other services, includes: serodiagnosis of meningococcal disease; meningococcal isolate confirmation and characterization; molecular characterisation of meningococci. From the MenRU, the reports on isolates/PCR are regularly sent to the CfI There, the data are maintained, collated analysed and published as annual reports, until recently in the Communicable Disease Report (CDR) and now available on the HPA website (http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1203008863952?p=1203008863952).

Streptococcus pneumoniae

The local NHS and HPA laboratories will perform the laboratory testing, including culture growth, for *S. pneumoniae*, on either blood or CSF in suspected cases of bacterial meningitis requested from clinicians. Further, all submissions for reference laboratory testing on *S. pneumoniae* from the laboratories across England and Wales are sent to the Reference Unit for streptococci, part of the Respiratory and Systemic Infection Laboratory (RSIL), which is based in the CfI, London. Similar to the laboratory surveillance of *N.Meningitidis*, the reports on isolates are then collated, analysed and reported annually.

- **HPA reconciled laboratory reports (RLR) on pneumococcal disease:**

Data from laboratory isolates from HPA laboratories, NHS microbiology laboratories, and the RSIL in England. The RSIL has actively collected pneumococcal isolates from patients with invasive pneumococcal disease since 1996. More details on reporting to and recording of laboratory reports is given in the previous Chapter, section 2.6.

Haemophylus influenzae type B

Laboratory surveillance for HiB is done through the routine reporting from the HPA labs and the RSIL, as above for S. *Pneumoniae.*

Listeria Monocytogenes

Local NHS / HPA microbiology laboratories report any confirmed cases of listeriosis to the national HPA CfI. The Food Safety Microbiology Laboratory (FSML) provides the national reference facility for the epidemiological typing and/or toxin testing of *L. Monocytogenes* along with a number of other organisms and other agents associated with foodborne infection and intoxication.

Mycobacterium Tuberculosis

Laboratory surveillance for *M. Tuberculosis* is done through the HPA Mycobacterium Reference Unit. The system and principles of reporting and surveillance there are similar to as described for *S. Pneumoniae* at RSIL.

Escherichia Coli

The HPA Laboratory of Enteric Pathogens (LEP) is the national Reference Centre for England and Wales for pathogenic enteric bacteria. The LEP receives bacterial isolates, and clinical specimens, as faeces and sera, from HPA, National Health Service and

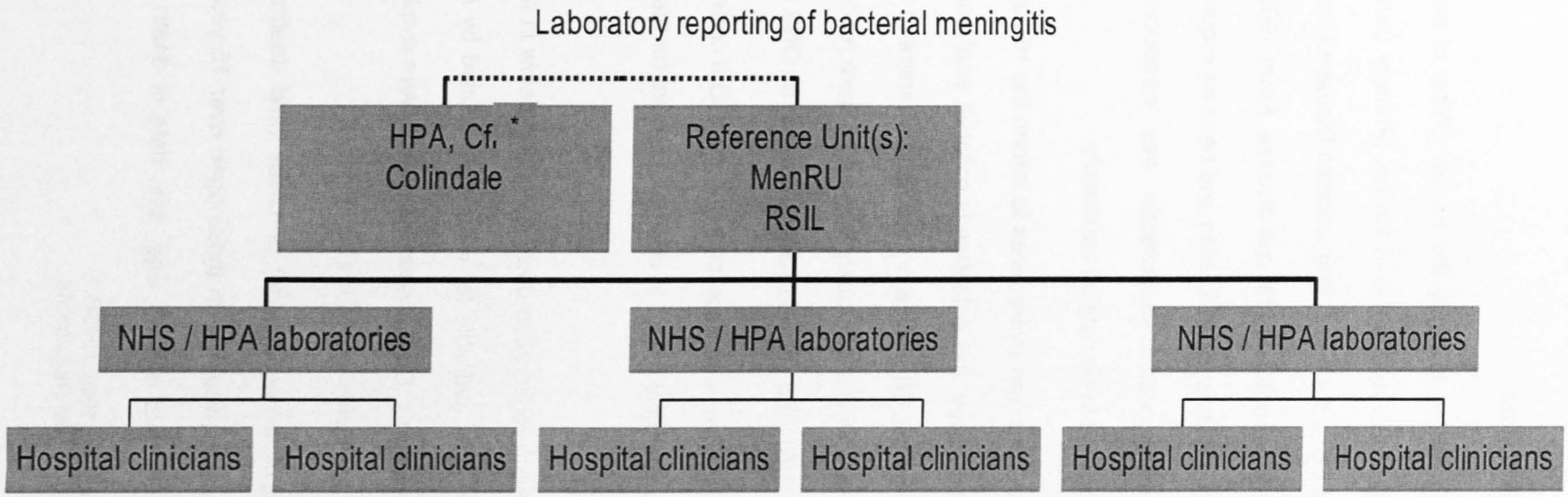
other laboratories throughout the UK. The LEP provides reference services for *Escherichia coli*, amongst other entheric pathogens.

- **Enhanced laboratory surveillance data**

Enhanced surveillance data from reconciled reports (routine laboratory and reference unit) on pneumococcal meningitis (ESPM) for the period 1996 to 2000 in cases aged over 15 years and individual information on causative organism, specimen type, date of birth, age, sex, earliest specimen date, reporting laboratory, region, outcome.

Enhanced surveillance data from reconciled reports (routine laboratory and reference unit) to CfI of meningococcal disease (ESMD) for the period 1996 to 2001 in cases aged over 15 years with individual information on causative organism, specimen type, earliest specimen date, age, sex, reporting laboratory, region and outcome.

Figure 3.1 - Diagram of laboratory reporting



** Centre for Infection*

b) Clinical notifications – ONS data

All clinicians are required by statute to notify the Proper Officer of suspected case of bacterial meningitis [3]. In most Local Authorities in the UK (Primary Care Trusts, PCTs), the proper officer is the local Consultant in Communicable Disease Control (CCDC). Up to 1968 all cases of meningitis were notified as one disease. From 1968 meningococcal meningitis was introduced as a distinct classification and became required to be notified separately. From 1989 meningococcal septicaemia was introduced as a distinct classification and became required to be notified separately.

The Proper Officers, then, are required every week to inform the HPAs CfI of details of each case that has been notified; and the data then is collated, analysed and published, as local and national trends by the CfI. Following the establishment of the CDSC these data started to be reported there, whilst previously these data were reported to the Office for National Statistics data (ONS), and still often are referred to as ONS notifications.

Information on the cause of disease was recorded using the ICD 9 coding system based on the diagnosis made by the medical officer in charge of patient (or the coroner in case of death).

The ONS notification (and death registration data, described below in the Mortality data section in this chapter) were only available for meningitis caused by *H. influenzae*, *S. pneumoniae*, and all *N. meningitidis*. Death registration data were available only from 1 January 1993 (see above 'Case Definition / Time').

I used the ONS reports (clinical notifications) of cases (and deaths) from bacterial meningitis and meningococcal septicaemia in those aged over 15 years 1993 – 2002, with information on ICD code, date of birth, age, sex, date of death, place of death,

[3] Public Health (Control of Disease) Act 1984. HMSO.
2. The Public Health (Infectious Diseases) Regulations 1988. HMSO.

Health Authority, NHS trust, Region. Data from this source, through separate extractions, were used in analyses in Chapter 4 and Chapter 5.

c) Hospital Episode Statistics (HES)

Medical information on all patients treated in or admitted to NHS Hospitals in England. Diagnoses are recorded using the International Classification of Diseases 10 (ICD 10) coding system based on the clinical diagnosis from the patient case notes, which may include local laboratory diagnostic data. An *'episode'* is identified as an admission at a time under the care of a consultant. If the patient moves under the care of another consultant, or is transferred to another hospital unit/department, even though for the same condition for which s/he was admitted, then each of these events is entered as a separate episode in the HES.

3.4.1. Mortality data

These were derived from: HES, ONS, or Laboratory reports.

- **HES**

The reporting system is described above. The death data from HES are used in the application of capture-recapture analysis; the method is described further in this Chapter, and the results are presented in Chapter 5.

- **ONS**

The reporting system is described above. The death data from ONS are used for estimates of mortality and case-fatality in: i) the review of epidemiology, and ii) in the application of capture-recapture analysis; the method is described further in this Chapter, and the results are presented in Chapter 4 and Chapter 5, respectively.

- **Laboratory reports**

The reporting system is described above. The death data from laboratory reports are used in estimates of case fatality rates in the review of epidemiology (results in Chapter 4), though generally the main estimates of the case-fatality rates are obtained from the ONS data for deaths, whilst using deaths from lab data to serve as comparison (unless otherwise stated).

a) Population Data

The population data for England and Wales is available from the census data. I used the mid year population estimates, by age, sex, region.

Data on age were available in 5 year age-group bands, e.g. 15-19; 20-24; 25-29, and so on to 85+. To retrieve the data for my study population, i.e. 16 years old and older, I divided the 15 to 19 age-group data by 5 and then multiplied this figure by 4 to get the population for the age-group 16 to 19. This assumes that the population in the age-group 15 to 19 is uniformly distributed. I deemed this to be a reasonable assumption.

c) Original data

Examining trends of lumbar punctures (LP) performed

In order to examine the extent of reliability of the data-sources, in particular the laboratory testing of the CSFs for CABM, I conducted a survey of the microbiology laboratories in the South West region. The objective of the survey was to collect the annual numbers of CSF specimens received by the laboratories for testing between 1991 and 2000 for 0 to 15 year olds and for those aged over 15 years and to compare this with the laboratory reports nationally. This was aimed as a validation exercise for the number of CSFs tested, to be compared against the national reports from the Laboratory surveillance on the CSFs. I wanted to compare the trends of the reports from the national surveillance for the SW region with the data collected from this survey. This was a postal / email survey and I followed up the returns / non-returns with telephone calls, as appropriate. This was part of the research done for Chapter 4.

Validation of data sources

To validate the diagnosis and matching in the data extracts, I sent the relevant data extracts, line listings of HPA RLR and HES, to the consultant microbiologists in 17 laboratories providing clinical microbiology services to all acute hospital trusts in the South West Region of England. I asked them to verify the correctness of diagnosis and matching according to their own laboratory records. They also obtained details from their local NHS Trust of hospital episode diagnoses of pneumococcal meningitis for cross checking against HPA RLR and HES records. This was done as part of the research for Chapter 5.

3.4.2 Data collection and management

3.4.2.1 Extraction of data

Laboratory reports

Laboratory confirmed cases were identified from the HPA laboratory reports database for England and Wales. Methods of confirmation included microscopy, culture, DNA or antigen detection from cerebro-spinal fluid (CSF) for meningitis, and culture or DNA detection from blood for septicaemia).

I requested and used the data on laboratory reports for cases of all forms of CABM (as specified above, 'Case definition / causative organism'). This specified the request for "laboratory reports from England and Wales on all specified forms of bacterial meningitis (CSF PCR and/or culture positive, all causes) and Neisseria meningitidis (blood PCR and/or culture positive) with dates of specimen between 1st January 1991 and 31st December 2002 for ages 16+. The data listed also specimen type, organism serotype/group, age/DOB, sex, laboratory, region and outcome."

ONS data

I requested the data on clinical notifications and deaths from England and Wales on CABM and MS classified by the ICD 9 codes as 320.0, 320.1 and 036 and any digit after with date of reporting between 1st January 1991 and 31st December 2002 for ages 16+. Data was listed for causative bacteria (serotype/group), age/DOB, sex, laboratory, region, outcome (died or not). Data was provided by the Information Officers at the CfI as an Excel spreadsheet.

All adults in England 16 years and older with a diagnosis of pneumococcal meningitis were identified in HES and HPA RLR for England for the incidence analysis, and HES and ONS for England for the mortality analysis. HPA RLR data for the year 2000 were

not available at the time of the study and the HES data were recorded as financial years 1996 – 1999. Therefore the incidence analysis was restricted to the period between April 1996 to December 1999. The mortality analysis was conducted using records from April 1996 to March 2000. For the case-fatality rate estimates, the mortality analysis was restricted to December 1999, to be comparable with the incidence analysis.

Cases were extracted from the PHLS RLR data where *S. pneumoniae* was isolated from CSF or when the clinical diagnosis recorded was pneumococcal meningitis.

Cases from HES were extracted when ICD 10: G001 was recorded in the main diagnostic field.

Cases were extracted from the ONS data were pneumococcal meningitis (ICD 9: 3021) was the primary cause of death.

HES data

HES data were available from the Department of Social Medicine, University of Bristol. I requested "All episodes with A170, A39(A39.0 toA39.9), G00(G00.0 to G00.9) in main diagnosis field for HES years 1996 to 2000, for adults aged 16 years and older, with information on HES year, NHS Region, Ward, Sex, Age, Date of birth, diagnosis code (ICD10) , date of start of episode, date of discharge, Trust name. All data was provided as encrypted Excel spreadsheet.

I used the HES data for the period 1996 to 2000 in cases aged over 16 years and individual information on causative organism, primary diagnosis (ICD 10), date of birth, age, sex, date of admission, date of episode start, episode end, discharge date, reporting NHS Trust, Health Authority, Region, date of start of episode (proxy for date of onset of disease), outcome. The HES data are used in Chapter 5.

3.4.2.2 Identification of Duplicates

Laboratory reports

The laboratory reports, including the RLR for pneumococcal meningitis may contain duplicates owing to multiple sampling for diagnosis. 2 or more PHLS RLR records were considered to be duplicates if they had same 'Date of Birth' and 'Sex', same 'Laboratory' and the laboratory specimen (CSF, blood, etc) had been collected within 3 months of each other. The earliest specimen was retained in further analysis.

HES

As mentioned above the HES contains data that often consists of many episodes of treatment of a patient for the same condition during the same admission at hospital. It is therefore clear that in order to use this data for estimating the incidence of a condition, in this case pneumococcal meningitis, much of the entries in the data-set would actually be multiple entries of the same incident case.

Duplicates were identified as follows: 2 or more HES records that had the same '*Date of birth*' and same '*Sex*', and that were within 3 months of each other. '*Hospital NHS Trusts*' were considered as a unique place identifier. However infectious diseases can reoccur (i.e. the same infection occurring at multiple episodes), though recurrent meningitis is not common. Therefore clear definitions of duplicate cases needed to be decided *a priori* when using these data. Records with different place identifiers but with the same '*Date of birth*', same '*Sex*' and within 3 months of each other were considered duplicates where a referral pattern between NHS Trusts (i.e. in the same or adjacent regions) could be identified. The record with the earliest '*Date of start of episode*' was retained from each duplicate set for analysis.

For reports with same *'Date of birth'*, '*Sex'*, '*Date of start of episode*' within 3 months but for whom there was no clear referral pattern I did two sets of analyses, as follows:

i) The main analysis, in which I included these reports as separate cases – these results are presented as the primary analysis (Chapter 5)

ii) A sensitivity analysis, using more stringent criteria, in which I entered these reports as just one case, retaining the report with the earliest date of hospital admission in the analysis.

ONS

The ONS data had the least amount of duplicates. These may occur due to reporting by different sources, or as artefact, e.g. errors in data reporting or entry . Two or more ONS records were considered to be duplicates if they had same 'Date of Birth', 'Sex', 'Date of Death' and 'Place of Death'.

3.4.2.3 Exclusions

Causative organisms

Meningitis caused by other bacteria that are more rare and are probably hospital acquired infections, such as forms of *Staphilocuccus*, Gram Neg bacilli / *Enterococci*, are not included.

From the ONS data I excluded ICD 9 320.8 and 320.9 (meningitis due to other specified bacteria and meningitis due to unspecified bacteria, respectively), as it is more likely that these would be hospital acquired rather than community acquired infections. These data were also available from the data officers at the CDSC, Colindale.

3.4.3 Data Confidentiality

All the data sets that contained identifiable information were provided and saved as encrypted or password protected files.

Ethical approval was not required for this part opf the study as the data were supplied under strict procedures of ensuring confidentiality, specifying the protection of the data and the purpose for the use of the data. The person identifiers were restricted to date of birth, sex and the unique identifier (HES , laboratory data).

3.5 The clinical management research

This part of the research addressed 2 of the main objectives of this thesis, objectives 3 and 4, and these methods relate to the results presented in Chapter 6 and Chapter 7. The 2 parts of this section are the review of clinical notes clinical management and the examination of the association of clinical practice with the outcome of CABM and MS. The latter uses largely epidemiological methods of measuring associations. However, as the data used and the aim for this objective, both result from the review of clinical notes study, it seemed appropriate to follow a common structure.

Data and research methods for the review of clinical management

3.5.1 Ethical Approval

The study was approved by the South West Multi-Centre Research Ethics Committee, reference MREC/01/6/70.

3.5.2 Study design

A retrospective review of clinical records of patients with CABM and MS in randomly selected hospitals in England and Wales.

Sampling frame: All acute NHS trusts in England and Wales.

3.5.3 Stages of the research

This part of the research was undertaken in three stages:

i) the pilot study

ii) the main national clinical records review

iii) the examination of association of management with outcome

3.5.4 The pilot study

I undertook a pilot study with the aim of testing the reliability and validity of the case-report form used for data collection in the main study. The pilot study was aimed, also, to test the feasibility of conducting the national review. The results and the experience from the pilot study were fed into the design of the main study. Results of the pilot study and how these informed the main study are shown in Chapter 6.

Pilot study - sample and data

The Hospital Trusts in the pilot study were enrolled as a convenience sample. The sample aimed to cover a range of geographical and clinical variation, including the following criteria:

- To include hospital trusts from at least two NHS administrative English regions;
- To include at least one NHS teaching hospital trusts;
- To include at least one big hospital, i.e. >= 600 hospital beds.

Case notes of all the cases identified in the enrolled hospitals were reviewed.

3.5.5 The main – national study

3.5.5.1 Sample and data

The first stage in the study was enrolment of hospitals, and then enrolment of cases within these hospitals (these cases constituted the study unit).

Enrolment of hospitals

There were a total of 188 Acute NHS Trusts across E&W of which 126 were general hospitals and 62 were specialty hospitals. Only the 126 general hospitals were eligible for inclusion.

Step 1: The sample was stratified by the 9 health regions of England and Wales. The primary sampling unit was the NHS healthcare trust and two trusts were randomly selected within each region.

Step 2: Hospital trusts usually consist of several different hospitals. Of all hospital trusts enrolled in the study, I selected the acute general hospital of the Trust for inclusion in the study since this would be where the patients with CABM and MS in adults would largely be treated.

Step 3: If there was more than one acute general hospital within a trust, one hospital was randomly selected.

Step 4: After the random selection a letter was sent to both, if different, the Medical Director for the Trust and to the Caldicott Guardian for the trust. The letter explained the purpose of the study and asked if they would be prepared to participate.

Enrolment of cases

- **Retrieving the case-notes**

After approval was obtained from the Medical Director / Caldicott Guardian, I contacted the Medical Records Managers to agree the dates for the site visit to review the case notes. I instructed the Medical Records Managers on the case definition (including the ICD10 codes and time period) for which they were to identify and retrieve the case-notes and make them available for my visit. A copy of the check-list for the process of enrolment, of both, hospitals and cases is shown in Appendix 4 (Trust sampled check list).

- **Case definition**

The case definition for the overall research is given earlier in this Chapter, section 3.2. However, there are some specific aspects for this part of the research. The inclusion of the cases was dependent on the final clinical diagnosis, with or without laboratory confirmation and on the study period for this part of the research covered slightly different years to those used for the epidemiology study (see Table 3.1). The cases included were:

Confirmed: meningitis septicaemia AND at least 1 of the following: i) Isolation of *N. meningitidis* or other bacteria from blood, CSF or skin rash; ii) bacteria seen in CSF, iii) *N. meningitidis* DNA in blood, CSF or rash; iv) *N. meningitidis* specific antigen in blood, CSF or urine.

or

Probable: meningitis, septicaemia in the absence of laboratory confirmation where bacterial meningitis and/or meningococcal septicaemia is thought to be the most likely diagnosis by the clinician managing the case and/or CCDC.

Cases were identified by discharge diagnoses with ICD 10 codes. Diagnoses reviewed included any of the following ICD-10: A39 (all, meningococcal infection), G00 (all bacterial meningitis).

All cases admitted to the hospital between 1st January 2000 to 31st December 2001 were included.

- **Plan for enrolling cases within the Hospital**

Following the arrangement with the medical records manager I visited the Hospital Trust and reviewed the medical notes using the standard case-form on-site, following these steps:

- Retrieve all cases (corresponding ICD codes) between January 2000 to December 2001
- If more than 16 cases available then randomly select 16 of them. The sample size will be discussed below, in section 3.6.11

- Exclusion criteria

The exclusion criteria for cases were:

- if transferred from another hospital
- if died before admission
- if onset of illness was 2 weeks or more after hospital admission
- any past neurosurgery
- immunocompromised individuals (HIV, chemotherapy, organ transplantation, chronic high doses of steroid therapy).

For the assessment of association of clinical practice with the outcome an additional exclusion criteria was cases that died within 6 hours of arrival at hospital.

3.5.6 Data collection

I collected the data using a standardised case-report form (questionnaire) developed for this study. The questionnaire was approved by the Expert Panel.

3.5.6.1 The case-report form (see Appendix 5)

The questionnaire was designed to incorporate all main areas of clinical management of CABM and MS cases including:

- Personal identifiers and demographic data
- Prehosptial management

- Admission to hospital
- First assessment
- Further diagnostic and treatment procedures
- Measures of disease severity such as Glasgow coma score (GCS), blood pressure, white blood count
- Specialist Vs non-specialist care
- Chronic cardiac, pulmonary, liver and renal disease
- Outcome (death, long-term sequelae)

The case-form was designed to record the times of the management procedures and allow for calculation of times between arrival / admission to management, length of stay, etc.

The questions on the above items included information on whether the indicators and procedures were performed (Y / N / NK) and the date & time; the outcome / result, as appropriate.

For consistency and reliability of data recording, I categorised and coded some of the text answers, such as the types of the antibiotics administered (e.g. Benzyl penicillin = 1, ..., vancomycin = 8, other =9), the grade of the clinician (JHO = 1, ..., Consultant = 4), the type of the sequelae (deafness =1, ..., amputation of limb = 7), etc.

Data on the size of the hospital and population coverage

I also developed a brief form to collect data on the size of the hospitals and the NHS Trust, the population coverage, and whether the hospital was a teaching hospital. These data were then merged with the data collected on clinical management for the respective hospitals / trusts and used in analysis for examination of clinical

management, e.g. classification of hospitals as big or not. The definition used was: a trust is considered to be large if it has more then 600 beds.

3.5.7 Data management

The data were entered by a data entry clerk based at the CfI, Colindale, London. The data were double entered to check for consistency and identify errors in the entry. I provided support, as needed, for the data entry.

Data was entered into a Stata v 6 data-base.

As the research fellow for the study I had the responsibility of data management, including maintenance, editing, clearing, standardising; with the approval of the Lead Investigator. Specific issues of data management were:

- In some cases a specific diagnosis was missing, and a general diagnosis of meningococcal disease (MD) was given. In these cases, for the purpose of the study (e.g. the definition of severity) I assigned a classification of the case as primarily meningitis or septicaemia based on the clinical picture. The features that I used to define the classification as either primarily meningitis or septicaemia were based on: the CSF results (indicative of meningitis), presence of rash (indicative of septicaemia), causative organisms (if other than *N. Meningitidis* would be meningitis). For classification of these cases I consulted with my external supervisors, Prof R. Heyderman and Prof J. Stuart.
- The laboratory result values were recorded in different measurement units at different hospitals. I standardised these units to the recommended standard

units for the laboratory results (e.g. the blood glucose or urea levels where recorded either as mg/dl or mmol/l , and I standardised them all to mmol/l [4])

3.5.8 Ensuring confidentiality

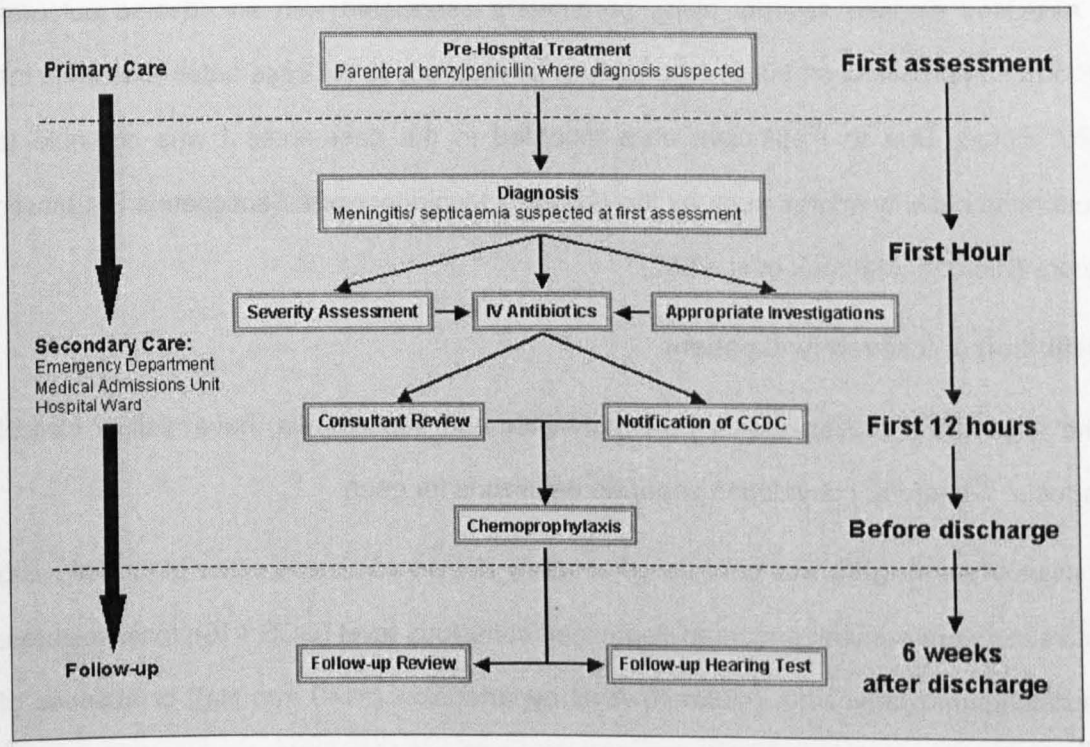
Each hospital trust, hospital and patient was given a code (an encrypted unique identifier) to maintain anonymity but to enable record linkage. I, the research fellow, was the only one to be able to identify the coded subjects, though for the cases I made no record of their names.

3.5.9 Assessment of standards of practice

I formulated the standards of clinical practice based on the British Infection Society (BIS) guidelines (Begg, Cartwright et al. 1999) , with the support of the study investigators and finally with the approval of the expert panel. Standards included all relevant aspects of disease management process such as: first assessment, management in the first hour through to follow-up, disease severity assessment and recording of clinical data. The standards provide an analysis framework for the study (Figure 3.2) and the results are compared against these recommended standards.

[4] http://en.wikipedia.org/wiki/Glucose_meter

Figure 3.2 - Clinical management of CABM and MS



Assessment of disease severity

I assessed disease severity using parameters associated with an adverse outcome (Riordan, Marzouk et al. 2002), and likely to be recorded in the case-notes (based on the pilot study). Due to insufficient data recorded in the case-notes I was not able to determine severity scores such as the Glasgow Meningococcal Septicaemia Prognostic Score (Riordan, Marzouk et al. 2002).

Definition of a severely ill patient

The two clinical presentations, i .e. meningitis and septicaemia, have distinct clinical aspects. Therefore, I developed separate definitions for each.

A case of meningitis was considered severely ill if on admission either of the following indicators were present: a marked depressed conscious level (GCS <10); focal seizures; papilloedema; bradycardia (<60/min) AND hypertension (>140 mm Hg); or absence of neck stiffness accompanied by a WCC <1 x 10^9L and a platelet count <100 x 10^9L (*definitions available in the* Appendix .3).

A case of meningococcal septicaemia was considered severely ill if either the admission systolic blood pressure was <90mmHg or Glasgow Coma Score was <10; or if three or more of the following were present - absence of neck stiffness, WCC <1 x 10^9L, platelets <100 x 10^9/L or $HCO_3 \leq 15$ mmol/L.

I also noted the extent to which severity had been assessed according to the clinical records, dividing this as fully or partially assessed as follows:

A case of meningitis cases was considered to have been assessed partially if an examination of pulse, blood pressure, conscious level (GCS) and focal signs was performed; and if in addition to the above the respiratory rate and papilloedema were also examined than this was considered as full assessment.

A case of septicaemia was considered to have been partially assessed if an examination of pulse, blood pressure, conscious level (GCS) was performed. If in addition to the above an examination of respiratory rate and peripheral perfusion (or signs of cyanosis) were also performed the case was considered fully assessed.

Assessment of outcome

I used the following endpoints to assess the clinical outcome of a case: death, length of hospital stay, and long-term sequelae (deafness, neurological deficit, major skin grafting or amputation).

Assessment of data quality

I determined the quality of data recording in the clinical notes, classifying as: '*good*' if more than 75% of essential information (as specified in the Appendix .3*)* was recorded; '*medium*' if 50% to 75% was recorded; and '*poor*' if less than 50% was recorded .

3.5.10 The examination of association of clinical management with outcome

This part of the research was conducted following the review of the clinical management with the aim of examining whether aspects of clinical management were associated with the clinical outcomes.

3.5.10.1 Definition of Outcome

Length of stay: A 'long Hospital stay' was defined as over 16 days. This outcome was dropped from analysis as found to be strongly correlated with 'Long-term sequalae' and the latter was preferred as more robust.

Good outcome: recovery; no long-term sequelae

Adverse (bad) outcome: defined as either death or long term sequelae.

3.5.10.2 Variables/ Confounders to control

The following variables are considered as confounders to the clinical management indicators in relation to outcome of the disease:

a. Age

b. Causative organism

c. Underlying medical conditions

d. Severity of illness signs/ symptoms:

- To identify predictive factors (clinical parameters associated with outcome) perform univariate analysis for all 'explanatory variables' (signs, symptoms, laboratory parameters) in data-set, report and control for those that are significant (95% CI).
- Predictive factors were identified from the univariate analysis).

3.5.10.3 Measuring the association

This examined the clinical management factors associated with outcome. I performed univariate analysis using logistic regression of the following variables with adverse outcome:

a. First assessment within 1hr of arrival

b. Antibiotics administered at first assessment

c. Diagnosis at first assessment

d. Consultant assessment with 12 hours of arrival

During the analysis for measuring these associations it became apparent that the missing data (i.e. data not available on clinical management indicators performed, in particular their timings) renders this part of the research uninformative as it was planned. Methods that I used to deal with the missing data are presented below in section

3.6 Statistical analysis

3.6.1 Calculation of rates

Incidence and mortality: Both incidence and mortality were calculated as number of events per 100,000 relevant population using mid-year population estimates for each corresponding year of the study (ONS: population Estimates Unit). The analysis was stratified by age, or age-group and year as appropriate. Incidence of the disease is relatively low and the immunity after infection is not long lasting. Therefore the number of prevalent cases was not deducted from the population at risk, but overall population was used. Calculations were performed using either Excel for Windows or Stata, as appropriate.

Case fatality: The case fatality rate was calculated as the ratio of number of deaths per relevant cases.

For **the review of the epidemiology** (results presented in Chapter 4), the case fatality rate is generally calculated using laboratory reports as source for cases and ONS as sources for deaths (see above 'Data sources), unless otherwise specified.

For **the capture-recapture analysis** (results presented in Chapter 5,), it is calculated using cases and deaths from the estimated numbers yielded from the capture-recapture for each data sources.

For **the review of clinical records** the case fatality rate was calculated using cases and deaths from the cohort of hospital cases included in the study.

Calculations were generally performed in Excel.

3.6.3 Poisson regression models

I used Poisson regression to examine changes in the incidence rate over time and also to study differences in rates by age-groups, gender and region. The Poisson regression formula can be written as:

$$Y \sim Poisson(R)$$
$$Log(R) = beta0+beta1.X1+log(N) \quad (3.1)$$

Where Y is the number of events in a population of size N units, R is the rate; β_0 is the baseline, i.e. the log of the rate in unexposed; β_1 is the log rate ratio associated with exposure; and X_1 is the exposure. This can be simplified to:

$$Log\ (Rate) = Baseline + Exposure\ log\ rate\ ratio \quad (3.2)$$

This model(Kirkwood and Sterne 2003) assumes that, given the exposure variables, events arise in a Poisson process over time, and hence that numbers of events in successive time intervals are independent.

3.6.4 The likelihood ratio test (LRT)

I used the LRT to choose between 2 nested models, i.e. to compare 2 models to see if one of them fits a particular dataset significantly better, and in particular to test for any statistical interactions (McCullagh and Nelder 1983; Shoukri and Pause 1999).

The LRT is only valid if used to compare models that differ only by the addition of one or more variables (i.e. nested). The LRT is based on the likelihood ratio statistics, namely:

$$LR = 2*(logL1-logL2) \quad (3.3)$$

Where Li is the maximised likelihood for model i, and model 1 is nested in model 2, that is, extends model 2. Under the null hypothesis that the additional parameters in model 1 are zero, this statistic follows approximately a chi-square distribution, with degrees of freedom equal to the number of additional parameters in model 1 (McCullagh and Nelder 1983; Shoukri and Pause 1999)

I have presented the results for, and used in subsequent analyses, the better fitting models where the evidence from LRT suggests a better fit for the data.

I also used the LRT to test for the presence of statistical interactions when examining the recent epidemiology of CABM and MS (results presented in Chapter 4). For example when examining the changes over time I used the LRT to measure the interaction with age. Similarly, for interactions between age and causative organisms.

3.6.5 Adjusting for over-dispersion

Over-dispersion is common when using Poisson regression models in analysis of population based surveillance data (Collett 1999). Over-dispersion occurs when the variance is greater than the mean of the Poisson model. A consequence of this is that the p-values will be too small and confidence intervals too narrow (McCullagh and Nelder 1983).

I initially checked for over-dispersion using Pearson's Chi-squared statistic and residual degrees of freedom in the Poisson model. These did not indicate a large degree of over-dispersion (i.e. they did not differ substantially), nonetheless, I also considered the following models to account for over-dispersed data.

3.6.5.1 Negative binomial regression models

I applied negative binomial regression (NBReg). The NBReg combines the Poisson distribution for the outcome within clusters (as surveillance data on CABM and MS might contain clusters) and the gamma distribution of the random variation between cluster means (McCullagh and Nelder 1983; Kirkwood and Sterne 2003). I used Stata™ version 7 software to fit these models. I then compared these analyses with the results from Poisson regression models.

The 95% CIs around the estimates retrieved from the two models, i.e. Poisson and NBReg, varied very slightly, in that NBReg resulted in slightly wider CIs.

I also familiarised myself with and considered in some analyses some other methods to control for possible over-dispersion, including:

- Zero-inflated Poisson regression
- Zero-inflated negative binomial regression

These models are useful if we suspect that zero counts are in some way special, eg reporting inertia, that is when low counts tend to be reported as null.

3.6.6 Logistic regression models

Logistic regression models are used for binary outcome data . The logistic regression model defines the probability of the binary outcome Y, P(y=1), in terms of exposure variables x, as:

$$P(y=1)=\frac{\exp(\beta 0+\beta 1 x)}{1+\exp(\beta 0+\beta 1 x)} \qquad (3.4)$$

I used logistic regression models to predict the binary category of outcome for individual cases. For example I employed logistic regression models in examining the association of clinical predictors with the outcome and the effect of clinical management indicators in the outcome

over and above clinical predictors (i.e. evidence of association of clinical management indicators adjusted for confounding by clinical predictors).

Examining the association of clinical predictors I used a backward stepwise regression, i.e. by beginning the analysis with a full model (all clinical predictor variables) and eliminating variables from the model in an iterative process, i.e. those not statistically significant dropping from the model in a step-wise sequence.

3.6.7 Multilevel modelling

In the analysis of the review of hospital management one issue which I considered addressing was allowing for multilevel analysis (H. Goldstein. 1995). This was because the data structure is complex, with cases clustered (nested) within hospitals that are stratified by region. This gives rise to a hierarchical data structure. In addition, some management policies apply at the hospital level.

I compared the standards errors (s.e.) from the multilevel modelling with the s.e. from logistic regression models allowing for hospital cluster (svyset command in Stata). However, in general, the s.e. between the 2 models did not very greatly, hence I preferred to continue using the latter, especially since data are sparse: 18 trusts, 207 cases i.e. about 12 cases per trust.

So generally, in the analysis I employed the clustering technique in logistic regression models, which allows for the specification of multiple strata and primary sampling unit identifiers, in this case the hospital trusts (Carolina population centre 2009).

3.6.8 Test for trend analysis

Generaly I used the Poisson and Logistic regression models to test for trends, e.g. age, year, the results of anlaysis presentedi n Chapter 4. In a few instances, I used the Chi-squared tests for measuring trends over time and age; e.g. capture recapture analysis, Chapter 5.

I used either the Epi Info 2002 software, or Stata, as appropriate for test for trend analysis.

3.6.9 Capture-recapture analysis

The capture-recapture method quantifies the degree of overlap between two or more sources to estimate the number of unobserved subjects by any source examined. The method consists of matching the records between two or more sources to determine the 'best estimated number' of cases / deaths in the population. I shall only use the method for 2 data sources (see Figure 5.1).

The number of unreported cases and the total number of cases in the population, for both incidence and mortality is estimated according to the following expression, and the actual estimateor is derived from Petersen (Hook and Regal 1995),

$$\hat{x} = \left(\frac{ac}{b}\right);\ \hat{N} = a + b + c + \hat{x} \qquad (3.5)$$

where *a*-number of cases reported to source A only, *b*-is number of matched cases, and *c*-number of cases reported to source B only, $\hat{x}$ is number of unreported cases by any source and $\hat{N}$ is estimated total number of cases in the population .

For each source, i.e. RSIL, HES, ONS, the sensitivity of the reporting systems was calculated as the number of cases/ deaths of pneumococcal meningitis reported to one source over the total number of cases estimated from the capture-recapture analysis.

3.6.10 Matching of cases between the data sources

HES and PHLS reconciled laboratory reports on pneumococcal disease (RLR) data for England were compared for the incidence analysis; and HES and ONS data for England were compared for the mortality analysis. HES data were available only for hospitals in England, this prevented an analysis based on a larger UK data set (see above, section 3.4.1).

For incidence estimates data from the ESPD and HES were matched to estimate the 'real number' of cases in the population and estimate the sensitivity of each system for incidence. Data sources were matched on date of birth, sex and date of first specimen with date of episode start (+/-30 days), further matched on reporting region. For mortality estimations data from HES and ONS were matched on date of birth, sex, and date of death, and further matching on reporting Health Authority.

3.6.11 Underlying assumptions for capture-recapture method

The underlying assumptions to be met for the capture-recapture method applied to two data sources to be valid are as follows (Faustini, Fano et al. 2000) :

b. **Independence of sources:** the probability of notification of one event of pneumococcal meningitis in one data source is not dependent on its probability of notification in the other data source.

c. **Equal catchability:** for each data source, all the subjects in the population have the same likelihood to be captured by that source. This means that the probability of notification of a case is not influenced by its characteristics (age, gender, circumstances of diagnosis) in each source.

d. **The population is closed**, or at least changes in population are not large over the study period.

e. Cases in each data source are **true cases** (i.e. the specificity of each surveillance system is high) and the matching method should identify true and only true matches between the 2 sources.

The validity of these assumptions, in our present application, will be discussed in Chapter 5.

3.6.10.1 Sensitivity analysis

In order to test the validity and reliability of the method used, I performed a series of sensitivity analyses.

I carried out the first sensitivity analysis using more or less stringent criteria for identification of duplicates, matching on the records using age and region instead of '*Date of birth*' and '*Hospital NHS Trusts*' as identifiers.

I also performed analysis based on all diagnostic fields, as opposed to the first diagnostic field for identifying the cases. The inclusion criteria for HES was all cases where pneumococcal meningitis (ICD 10: G001) was recorded in any of the diagnostic fields in the HES data-base, and not just the main dg field. The rest of the criteria, including the selection of duplicates remained the same as for the main analysis.

3.6.11 Sample size calculations for the review of clinical management

The sample size calculations have been done separately for two main outcomes partly based on the pilot study (48 cases in total):

I. the proportion of cases with a suspected diagnosis at first assessment (within 6 hours of arrival); and

II. the proportion of with a suspected diagnosis at admission who are given parenteral antibiotics within 1 hour of admission.

For outcome I, 75% of cases had known outcome (37 out of 48)

Table 3.2 – Review of clinical management - outcome I: proportion of cases with a suspected diagnosis at first assessment

	Differential diagnosis≤6hrs			
NHS Trust	**No**	**Yes**	**Total**	**Proportion**
Jd1h	0	3	3	1.00
Jb1f	4	7	11	0.64
Jc1g	4	6	10	0.60
Ja1e	4	9	13	0.69
Total	12	25	37	0.68

An estimate of the variance of the proportion between trusts can be taken from the variation between the 3 trusts: Jb1f, Jc1g, Ja1e (as the first trust had unusually small number of cases) (sd=0.045).

An estimate of the overall proportion was taken as the average of the 3 trusts: Jb1f, Jc1g, Ja1e (mean=0.643).

Assuming these results, from the full study of n trusts, the 95% confidence interval for the overall proportion can be estimated as:

$$\bar{x} \pm t_{\nu=n-1} \frac{s}{\sqrt{n}} \qquad (3.9)$$

then the 95% CI of the proportion of cases:

If n=18 trusts: 0.64 [0.62, 0.67] If n=27 trusts: 0.64 [0.63, 0.66]

If I apply a sensitive analysis of an underestimation of the standard deviation between trusts by 50%, so that the true standard deviation is 0.09, then if n=18 trusts then the 95% CI of the proportion of cases: 0.64 [0.60, 0.69]

For outcome II, incompleteness is partly due to incompleteness in outcome 1:

Table 3.3 – Review of clinical management - outcome II: proportion of with a suspected diagnosis at admission who are given parenteral antibiotics within 1 hour of admission.

	Parenteral antibiotics≤1hr		If suspected diagnosis=Yes*	
NHS Trust	**No**	**Yes**	**Total**	**Proportion**
Jd1h	1	2	3	0.67
Jb1f	0	6	6	1.00
Jc1g	1	3	4	0.75
Ja1e	2	5	7	0.71
Total	4	16	20	0.79

An estimate of the variance of the proportion between trusts can be taken from the variation between the 4 trusts (sd=0.149).

An estimate of the overall proportion can be taken as the average of the 4 trusts: (mean=0.78).

Assuming these results, from the full study of n trusts, the 95% confidence interval for the overall proportion was estimated as:

$$\bar{x} \pm t_{v=n-1} \frac{s}{\sqrt{n}} \qquad (3.10)$$

then the 95% CI of the proportion of cases:

If n=18 trusts 0.78 [0.71, 0.86] If n=27 trusts: 0.78 [0.72, 0.84]

If for some reason there's been and underestimated standard deviation between trusts by 50%, so that the true standard deviation is 0.09, then if n=18 trusts then the 95% CI of the proportion of cases: 0.78 [0.63, 0.93].

As the primary aim of this study was to review the extent to which the BIS guidelines are met, a surrogate for the sample size was to accurratley estimate the proportion of cases with a quick (in 1 hour) diagnosis and treatment , hence a sample of 18 trusts was a sufficient sample. I should note that at this stage of study desing I had not developed the idea for investigating factors that might influence the outcome of the disease (CABM and MS in adults).

3.6.12 Measurement of clinical management

I measured clinical practice against the study standards, adjusted to allow for:

- stratification by region;
- the clustering of the sample within hospitals;
- within hospital correlation.

I included a weighting for the total number of cases reported in England and Wales in 2000; and the results in comparison of unweighted and weighted analysis are presented in Chapter 6, Table 6.6. As the distribution of the sample was close to the distribution of the national data (presented in Chapter 6, Figure 6.1), there was little difference between the weighted and unweighted numbers. Hence, the results following Table 6.6 are therefore reported unweighted, unless otherwise specified. Unrecorded data were omitted from the calculations unless otherwise stated.

I used the Standard Error (SE) of the estimate to determine the fitness of models with weighting and allowing for clustering effect asopposed to straight logistic regression model; sp that if these adjustments (i.e. wighting and /or clustering effect) resulted in the mode provducign a larger SE

– then these results are presented. Clinical practice was measured in terms of percentage of the standards met and its 95% confidence intervals. The associations between adverse clinical outcome and the recommended management practices were assessed using multiple regression models to calculate the risk ratios, controlling for severity of illness and age.

I used the median to summarise time differences between events and clinical measurements (the chronology of clinical practice) and the middle 50% of observations ("the interquartile range") to summarise variability. The times to clinical practice were calculated either from arrival or admission, as clinically relevant and were calculated in both times in minutes ('time to') and days ('days to') as per recommended standards. Where exact times were not available for much of the data (missing data on exact times of clinical practice) I made a judgment on the clinical and statistical relevance , and presented the results accordingly (i.e. either models with more subjects included – in 'days to' or the models with fewer subject, but more precision, - in 'time to'. The analyses was performed using Stata (v 6 to v 8) .

3.6.12.1 Calculation of 95% confidence intervals

95% confidence intervals (CI) were calculated and presented to validate the precision of the estimates.

For **the review of the epidemiology** the 95% CIs were retrieved from the Poisson/ Binomial regression models.

For the capture recapture analysis a parametric bootstrapping method was used to calculate 95% CIs for the estimated unreported number of cases, the estimated total number of cases in the population and the estimated sensitivities of the two data sources. 10,000 simulated results were derived assuming independent random variables for the number of records in the first data source but not in the second; the number of records in the second but not in the first; and for the number of records found in both data sources. These were assumed to follow Poisson

distributions with means equal to the observed counts. The 95% CIs were derived from the 2.5% and 97.5% percentiles of the simulated values. For the case-fatality rate in capture-recapture analysis the CIs are derived from the Poisson model.

For **the review of hospital management** the 95% CIs were usually derived from the regression models and were adjusted to allow for the clustering of the sample within trusts.

Similarly, for the examination of association of clinical management with the outcome the 95% CIs were derived from regression models employed.

3.6.13 Dealing with missing data

Due to incomplete recording of clinical practice in the clinical notes the missing data was an important determinant in my research methods. I used different approaches to dealing with missing data, and that:

i) using continuous variables (per hour; rather than binary Yes / No) time to first assessment for the following variables:

- time to first assessment
- time to antibiotics
- time to diagnosis
- time to consultant assessment
- time to ICU assessment

ii) Assuming best and worst scenario for the subject with no data regarding the performance of the clinical management indicator (Bridewell, Langley et al.; Collaboration 2002; Gamble and Hollis 2005). I treated the missing data in two subsequent approaches:

Best scenario: assumed that subject that had no data on whether a clinical indicator was performed and its time interval when performed had actually undergone that clinical

management indicator within the recommended time. e.g. for missing data on whether diagnosis made in the first hour from arrival in this scenario I assumed this as a positive entry. I then employed logistic regression models to examine the association of these indicators, in turn, with the outcome of CABM and MS.

Worst scenario: I assumed that subject that had no data on whether a clinical indicator was performed and its time interval when performed had not undergone that clinical management indicator within the recommended time. E.g. for missing data on whether diagnosis made in the first hour from arrival in this scenario I assumed this as a negative entry. I then employed logistic regression models to examine the association of these indicators, in turn, with the outcome of CABM and MS.

Chapter Four

The recent epidemiology of community acquired bacterial meningitis and meningococcal septicaemia amongst adults in England and Wales, 1991- 2002

Table of content

4.1 Introduction to Chapter 4

This chapter examines the epidemiology of community acquired bacterial meningitis (CABM) and meningococcal septicaemia (MS) amongst adults in England and Wales, for the period 1991 to 2002.

I have used data that is routinely available through the different surveillance systems in England and Wales for the major causes of bacterial meningitis. There are several different surveillance systems in place for these conditions, such as: the clinicians' notifications; laboratory reports, which include enhanced surveillance and the reconciled laboratory reports for *Neisseria meningitidis* (NM), *Streptococcus pneumoniae* (pneumococcus).

As usual with surveillance data, I have encountered difficulties, primarily with the timeliness, but also the completeness and other data quality issues. I will address these issues in the discussion section of this Chapter.

I performed the initial analysis of the epidemiology data during 2003, including the data for the period January 1990 to December 2000. In 2005 I undertook an update of the analysis, which includes data up to December 2002.

In this Chapter I firstly give a brief background of the epidemiological examination of bacterial meningitis. The data and methods applied are described in Chapter 3, section 3.4. I then present the results of this study, followed by a discussion of the study limitations.

In the first part of the results I have presented the examining the epidemiology of bacterial meningitis in a greater detail - by causative organisms, age, sex, and season. I also present some results of the analysis using methods to account for over dispersion and compare these to the Poisson regression methods.

This part of my research was published as a peer-reviewed article, reference: Gjini, A. B., J. M. Stuart, et al. (2006). "Changing epidemiology of bacterial meningitis among adults in England and Wales 1991-2002." Epidemiol Infect 134(3): 567-9.

4.2 Background: the rationale for examining the epidemiology of CABM and MS in adults

Understanding the epidemiology of CABM and MS is essential to appropriate clinical management and vaccine implementation. In order to begin to understand the burden of a disease it is usual to start by examining and describing its epidemiology. Therefore the information resulting from this Chapter has been essential to the further work I have undertaken through out my PhD research, which is presented in the following chapters.

Amongst children, CABM and MS are important infectious causes of death and disability worldwide (Noah 1987; Bedford, de Louvois et al. 2001; Fellick and Thomson 2002). As mentioned in the Background, during the 90s, new protein-conjugate vaccines against *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC) have had a dramatic effect on the epidemiology of childhood meningitis in several industrialised countries, including the United Kingdom (Ramsay, McVernon et al. 2003),(Ramsay, Andrews et al. 2003). Also, more recently, improvements in clinical management to paediatric meningococcal sepsis in particular, have been associated with a reduced mortality (Booy, Habibi et al. 2001).

The epidemiology of CABM and MS amongst adults, however, over this time period has been less well documented. It is uncertain whether an increasingly ageing population, a paediatric population with a vaccine reduced carriage of common causative pathogens and the resurgence of infections such as tuberculosis, have modified the spectrum of disease (Mohle-Boetani, Ajello et al. 1993; Barbour, Mayon-White et al. 1995; Sigurdardottir, Bjornsson et al. 1997; Wenger 1998; Rose, Watson et al. 2001; Grange and Zumla 2002). Also, as the incidence of bacterial meningitis in children declines, the relative public health importance of bacterial meningitis in adults increases (Durand, Calderwood et al. 1993; Butler, Shapiro et al. 1999). Recognition of these changes is important to inform clinical management and vaccination strategies. I have

therefore set out to examine the recent epidemiology of bacterial meningitis and meningococcal septicaemia amongst adults in England and Wales between 1991 and 2002.

4.3 Data and Methods

For full details of the data and methods see Chapter 3. Here I will just mention briefly the data sources and the statistical methods used. I have used the surveillance data from the laboratory reports and clinical notifications

Incidence – The primary source of data for incidence calculations was the laboratory reports. Clinical notifications are presented in one section as a comparison to laboratory reports.

Case-fatality – The primary sources for case-fatality calculations were: laboratory reports for cases and clinical notifications (ONS) for deaths. Case-fatality using clinical notifications for both sources of cases and deaths is presented in one section as comparison.

Population Data - The population data for England and Wales is available from the census data. I used the mid year population estimates, by age, sex, region.

Statistical analysis - I used the Poisson regression to calculate the incidence rates and the Negative binomial regression to account for the possible over-dispersion. The details of the methods used are presented in Chapter 3, sections 3.6.3 and 3.6.4.

4.4 Results

4.4.1 Incidence

Laboratory reports - There were a total of 3169 laboratory reports of CABM and 3118 (49.6%) of MS between 1991 and 2002 among adults in England and Wales.

The pathogen most commonly associated with community acquired bacterial meningitis among adults overall was *N. meningitidis* (70.7% of cases), followed by *S. pneumoniae* (19.2%), *E. coli* (2.7%), *M. tuberculosis* (2.8%), *H. influenzae* (1.9%), *L. monocytogenes* (1.9%), and GBS (0.7%).

Table 4.1 shows the number of reports by causative organism over the years.

	Year												
Causative organism	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**Grand Total**
E. coli	14	22	9	13	10	13	15	13	16	19	31	10	185
H. influenzae	13	23	6	13	19	10	12	4	8	6	8	10	132
L. monocytogenes	19	15	9	7	13	16	11	10	8	4	8	7	127
M. tuberculosis	10	10	14	10	5	19	18	12	19	19	28	28	192
S G B	6	4	6	4	6	3	2	2	4	4	2	6	49
S. pneumoniae	147	156	138	112	113	116	112	76	112	78	71	76	1307
N.meningitidis (blood)	291	263	266	214	304	345	404	380	404	375	310	251	3807
N.meningitidis (CSF)	110	107	81	70	93	103	83	101	82	67	61	45	1003
CABM and MS	610	600	529	443	563	625	657	598	653	572	519	433	6802

4.4.1.1 Incidence

During the twelve year period the overall incidence for CABM and MS was 16.9/100,000. For the twelve year period, the reports for *N. meningitidis*, both CSFs and blood isolates, showed the highest incidence, of 16.4/100,000 (with a peak of 1.8/100,000 in 1997), and within this the

incidence for meningococcal meningitis alone was 2.5/100,000. *S. pneumoniae* followed with a total cumulative incidence of 3.2/100,000 and the rest of the causative organisms all had an overall cumulative incidence of 0.48/100,000 (*M. Tuberculosis*) to 0.12/100,000 (GBS).

Changes over time

Overall the incidence CABM and MS in England and Wales has increased during the period 1991 to 2002. However, the trends differ for the CABM and MS in that decreasing for the former and increasing for the latter.

Overall there was a statistically significant decease in the incidence rate of bacterial meningitis. Decreases in meningitis due to individual organisms were seen for *N. meningitidis*, *H. influenzae* , *L. monocytogenes* and *S. pneumoniae* (Figure 4.1.a,1b). There was a mean annual increase of 11% in meningitis caused by *M.tuberculosis.* The decreasing trend in incidence of meningococcal meningitis contrasted with an increasing trend in meningococcal septicaemia (mean annual change -3% and 7%, respectively).

Figure 4.1.a) - Incidence of CABM and MS over time.

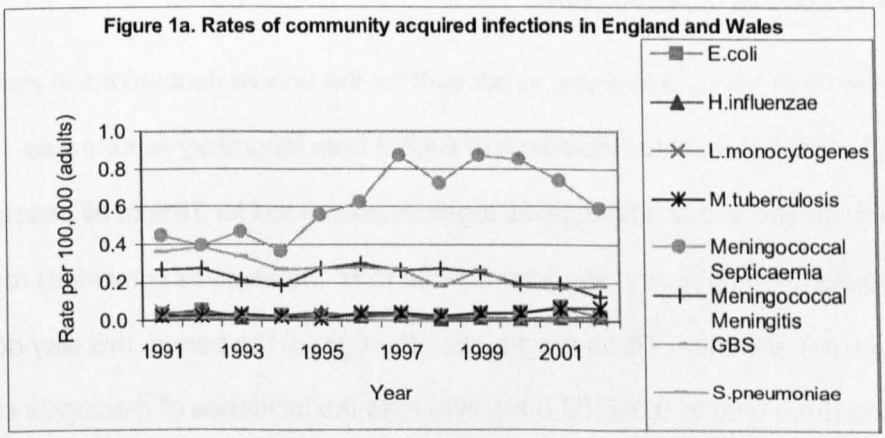
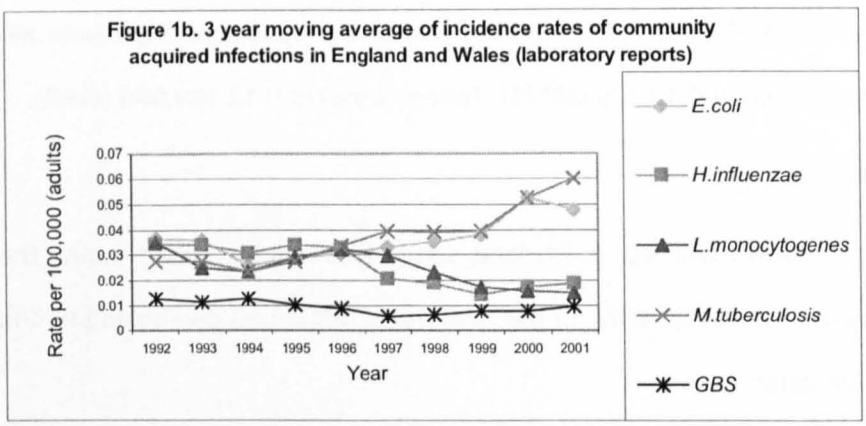


Figure 4.1.b) - Incidence of CABM and MS over time. – the less common organisms



Comparing trends in incidence with notifications of meningococcal meningitis and septicaemia, no significant trend in incidence of meningococcal meningitis was seen (RR 1.02, 95% CI 0.99 to 1.01, p = 0.2), but incidence of septicaemia also increased. Mean annual incidence rate was over three times higher for notifications of meningococcal meningitis than for laboratory reports (0.92/100,000 vs 0.24/100,000), but were similar for meningococcal septicaemia (0.63/100,000 vs 0.54/100,000), and for meningitis due to *S.pneumoniae* (0.26/100,000 vs 0.28/100,000) and *H.influenzae* (0.03/100,000 vs 0.04/100,000).

Table 4.2 present the three-yearly averages, to account for the annual fluctuations in incidence. For the period 1991 - 2002, the annual incidence of CABM from laboratory reports was 0.6/100,000. *S. pneumoniae* and *N. meningitidis* together accounted for 78% of all cases. Meningococcal disease (meningitis and septicaemia due to *N. meningitidis* combined) rose to a peak in 1997-99 and then declined. TB meningitis rose throughout the period; this way doubling over the study period (from 0.03 to 0.06/100,000). Whereas the incidence of meningitis caused by *S. pneumoniae*, *H. influenzae* and *L. monocytogenes* showed an overall decreasing trend over the study period.

Mean annual incidence rates were over three times higher for notifications of meningococcal meningitis than for laboratory reports (0.92/100,000 vs. 0.24/100,000) but were similar for other infections.

Table 4.2 - Incidence (per 100,000) of bacterial meningitis and meningococcal septicaemia in adults in England and Wales 1991 - 2002.

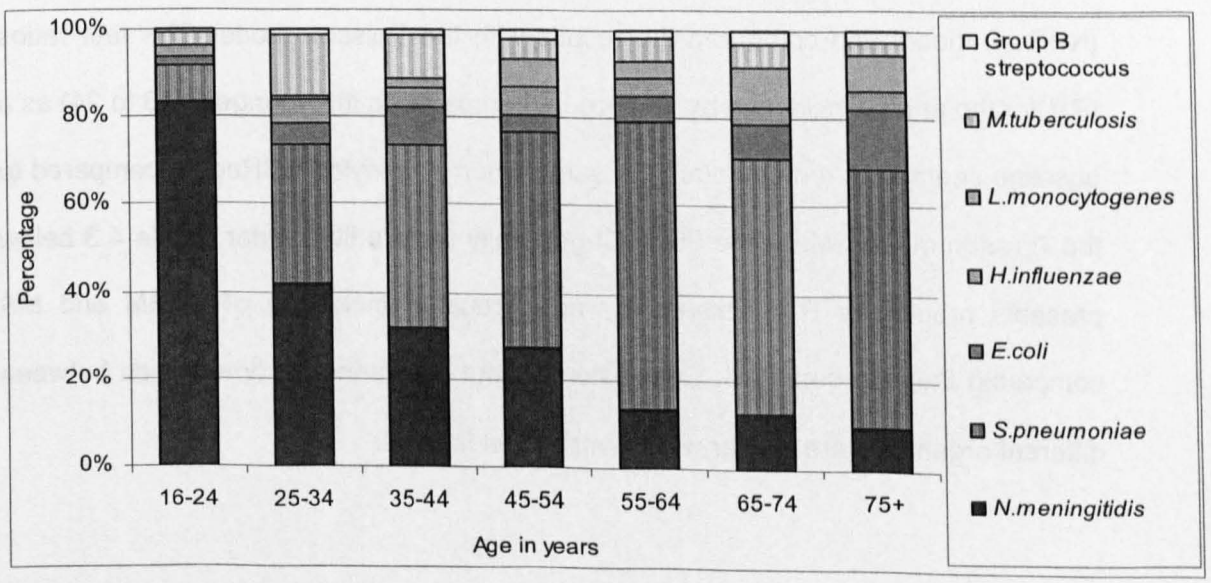
Organism	Rate/per 100,000 (n) 1991 - 1993	1994 - 1996	1997 - 1999	2000 - 2002	1991 - 2002	Annual average change RR (95% CI)
Bacterial meningitis						
Escherichia coli	0.04 (45)	0.03 (36)	0.04 (44)	0.05 (60)	0.04 (185)	1.03 (0.97 to 1.09)
Haemophilus influenzae	0.03 (42)	0.03 (42)	0.02 (24)	0.02 (24)	0.03 (132)	0.92 (0.87 to 0.99)
Listeria monocytogenes	0.04 (43)	0.03 (36)	0.02 (29)	0.02 (19)	0.03 (127)	0.92 (0.87 to 0.97)
Mycobacterium tuberculosis	0.03 (34)	0.03 (34)	0.04 (49)	0.06 (75)	0.04 (192)	1.11 (1.06 to 1.15)
Neisseria meningitidis	0.25 (311)	0.26 (316)	0.27 (332)	0.17 (218)	0.24 (1177)	0.97 (0.94 to 1.00)
Group B Streptococcus	0.01 (16)	0.01 (13)	0.01 (8)	0.01 (12)	0.01 (49)	0.96 (0.88 to 1.04)
Streptococcus pneumoniae	0.36 (441)	0.28 (341)	0.24 (300)	0.18 (225)	0.26 (1307)	0.93 (0.92 to 0.95)
SUBTOTAL	0.76 (932)	0.66 (818)	0.63 (786)	0.50 (633)	0.64 (3169)	0.96 (0.94 to 0.98)
Meningococcal septicaemia	0.44 (533)	0.52 (638)	0.82 (1032)	0.73 (915)	0.63 (3118)	1.07 (1.03 to 1.11)
TOTAL	1.20 (1465)	1.18 (1465)	1.45 (1818)	1.23 (1548)	1.27 (6287)	1.01 (0.99 to 1.03)

4.4.1.2 Causative organisms

The causative organism most commonly associated with bacterial meningitis was *S.pneumoniae* (41% of all cases of CABM), followed by *N. meningitidis* (37%), *M.tuberculosis* (6%), *E.coli* (6%), *H.influenzae* (4%), *L.monocytogenes* (4%) and Group B *streptococci* (2%).

The predominant pathogen associated with CABM varied according to age-group. The main pathogen responsible for meningitis in young adults remained *N. meningitidis*, comprising 84% (652/780) of cases in 16 – 24 year olds (Figure 4.2). This proportion decreased with increasing age to 10% (31/322) in over 75 year olds ($p<0.0001$). By contrast, the equivalent proportions for *S. pneumoniae* increased from 8% (63/780) to 59% (190/322, $p<0.0001$), and for *E. coli* from 2% (16/780) to 13% (43/322, $p<0.0001$). Analysis of age-specific incidence revealed a significant increasing trend with age for *E. coli*, *L. monocytogenes and S. pneumoniae* and Group B streptococci (all p values <0.001).

Figure 4.2 - Proportionate distribution of causative organism of bacterial meningitis by age.



Incidence of CABM and MS by age

The median age of adult patients with CABM and MS in England and Wales shifted from 31 years in 1991 to 40 years in 2002. In 1991 1.4% of cases occurred among those aged 85 years and older compared to 4.1% in 2002 ($p<0.0001$) whereas amongst 16-24 year olds there was a decrease from 44% of cases in 1991 to 32% in 2002 ($p=0.002$).

The highest incidence of meningocoocal meningitis and septicaemias occurred in young adults. Both laboratory reports and clinical notification data showed a sharp drop in incidence from the 16 – 24 to 25 – 34 years age groups (2.9 to 0.7/100,000 and 5.0 to 1.4/100,000 respectively) then subsequently little change with increasing age. There was a significant increasing trend with age for *E.coli, L.monocytogenes, S.pneumoniae* ($p<0.0001$) or Group B streptococci ($p = 0.001$). No significant trend with age was observed for *H.influenzae and M.tuberculosis.*

Comparing the results using Poisson with Negative Binomial regression models

To check and adjust for over dispersion I used the Negative Binomial Regression (NBReg) model and compared the results with the Poisson model. The rate ratios (RR)for the annual incidence by age group, compared to the youngest (16 to 24) as a baseline seemed to remain much the same when employing NBReg as compared to the Poisson model, whilst the 95 % CI generally were a little wider. Table 4.3 below presents results for RR increase by age group in incidence of CABM and MS comparing these two models. Conclusions about differences in time trends between different organisms are similar whichever model is used.

Table 4.3 - Rate Ratio for age group incidence comparing the Poisson and NBReg models. The youngest age group, 16 to 24 years old, is used as baseline.

	Poisson model		Negative Binomial Regression model	
Age group	RR	95% CI	RR	95% CI
16-24	1.000	1.000	1.000	1.000
25-34	0.271	0.253 to 0.290	0.271	0.220 to 0.333
35-44	0.234	0.218 to 0.251	0.234	0.190 to 0.288
45-54	0.287	0.269 to 0.307	0.287	0.232 to 0.353
55-64	0.228	0.212 to 0.245	0.228	0.185 to 0.281
65-74	0.218	0.203 to 0.235	0.218	0.177 to 0.269
75-84	0.163	0.150 to 0.177	0.163	0.132 to 0.202
85+	0.062	0.055 to 0.071	0.062	0.049 to 0.079

Incidence of CABM and MS by sex

Male/female status by age was available for 6182 (98.3%) of cases. Overall men were at a lower risk of acquiring the disease than women (rate ratio =0.94; 95% CI 0.89 to 0.99, p= 0.01). The sex difference in incidence rates changed with age such that in younger age -groups incidence was greater for men, but in older age-groups the incidence was greater for women (p for interaction <0.0001)

4.4.1.3 Case-fatality

The case-fatality rates were calculated as the proportion of deaths within the number of cases in the appropriate group, i.e. causative organism, year of reporting, age, etc. As stated in Chapter 3, Data and Methods, generally the data sources are: cases from the laboratory reports, and deaths from the ONS notifications, unless stated otherwise (this was done with the aim of comparing data sources).

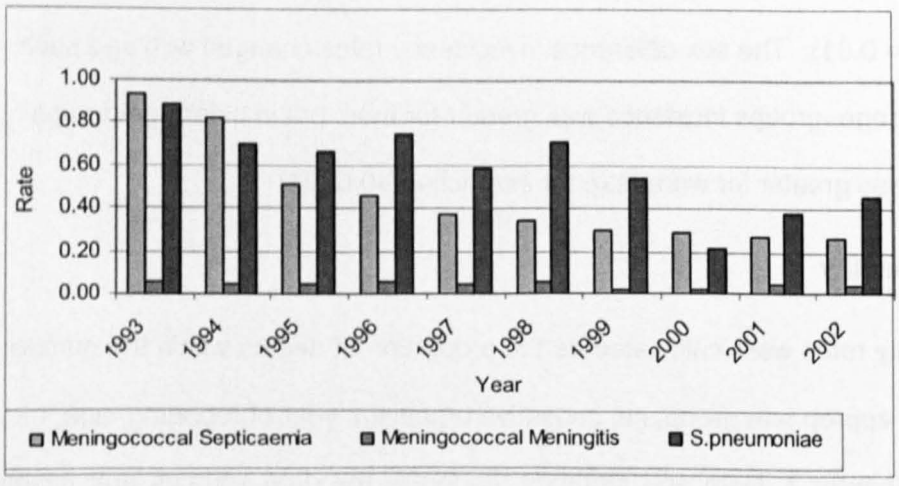
Pneumococcal meningitis had the highest case-fatality during the study period whether laboratory reports or notifications were used as the denominator (Table 4.4).

Estimated case-fatality rates for pneumococcal meningitis during the 10 year period fell from 69% in 1993/94 to 52% in 2001/02 (172/250 to 76/147, p<0.0001). Mortality rates showed a similar downward trend to that for case fatality, falling from 0.21/100,000 to 0.09/100,000 in the same period (p<0.0001).

Case-fatality rates for meningococcal septicaemia also decreased over the same period (48% to 27%, p<0.0001) but the case fatality rate for meningococcal meningitis remained at about the same level (22%). Overall mortality rates for pneumococcal and meningococcal meningitis (including meningococcal septicaemia) fell from 0.45 to 0.31/100,000 (p=0.0001) during a time when the combined incidence rates were not falling.

Case-fatality rates for TB meningitis also fell, from 83% (20/24) in 1993/94 to 34% (19/56) in 2001/02 (p<0.0001), mainly due to falling mortality in under 65 year olds.

Figure 4.3 Case fatality rates over the years

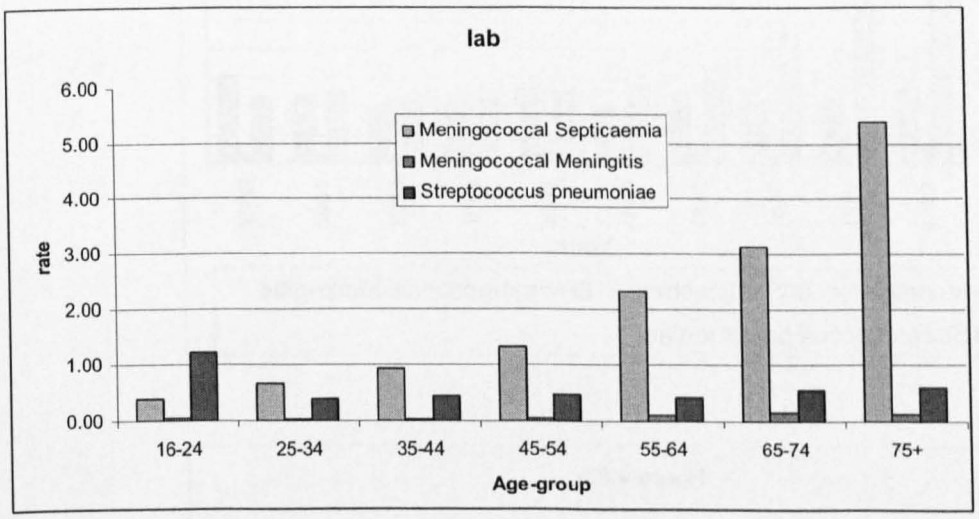


Case fatality by age

Case-fatality rates increased with age, whether derived using the laboratory reports as a source for cases, or when using the clinical notifications (X^2 7 DF, p=0.03 and p<0.001, respectively).

Among the older age-groups case-fatality rates decreased over time, but not so for the younger ages. The annual rate ratio of case-fatality rate for those aged 55 years and older as compared to 16-54 was 0.7 (p for interaction between age and time =0.018).

Figure 4.4 Case fatality rates by age group



4.4.1.4 The case fatality rate using different data sources

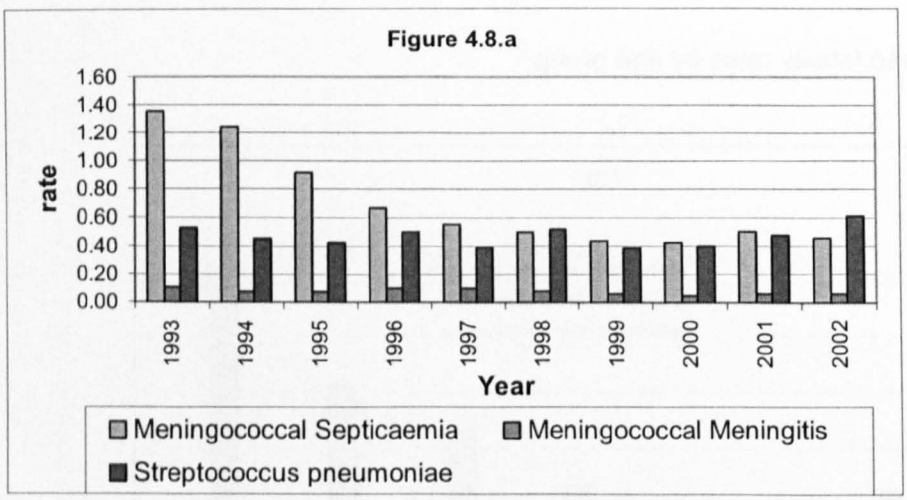
Whether using clinical notifications or laboratory reports as a source of data, for either cases or deaths, the case-fatality rates vary. As described in Chapter 3 the primary source of data in this study has been laboratory reports for incidence data and ONS notifications for mortality data. Below I will show some key variations in case-fatality rates estimated when using ONS data as source for incidence.

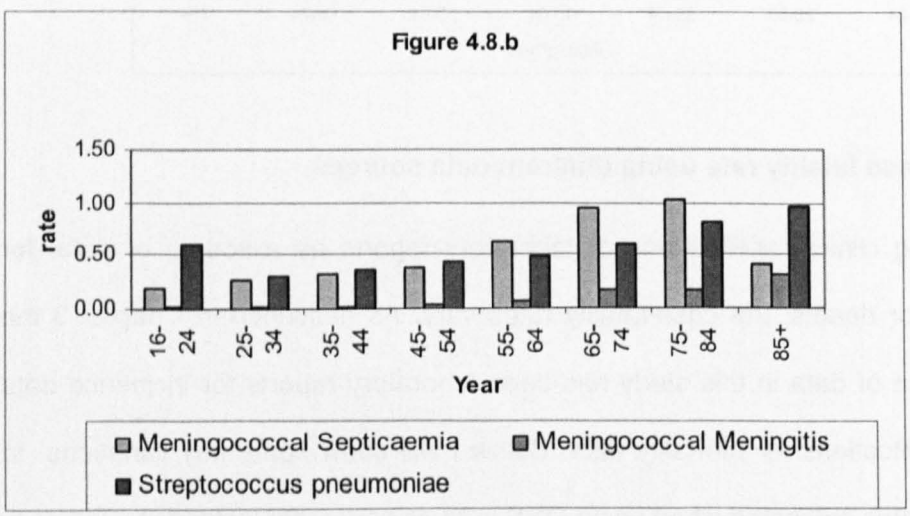
Using clinical notifications for both deaths and cases

Using the number of cases reported through the clinical notifications (ONS) (as opposed to laboratory reports previously) there are two differing features and that:

- The case-fatality for MS in the early 1992 and 1993 is over 100% - suggesting more deaths are reported as caused by MS than there are cases.
- the apparent drop in the case-fatality for those aged 85 years and older (Figure 4.8.b).

Figure 4.5 - Age-specific case-fatality rates. *Source clinical notification cases and deaths.*





Similar to the case-fatality rate when using laboratory reports for cases, the case-fatality rate for meningococcal meningitis/ septicaemia and pneumococcal meningitis

increased with increasing age from 21% in 16 – 24 year olds to 74% in the 75+ age group ($p<0.0001$).

Overall the largest difference in the case-fatality calculated when using clinical notifications as source for cases as opposed to laboratory reports was for meningococcal meningitis and that being lower (Table 4.4).

Table 4.4 Comparing case-fatality rates laboratory vs ONS reports.

Case fatality rates based on laboratory reports for the period 1993 - 2002 (numbers in brackets)			
Organism	**Total Deaths**	**Laboratory Report CFR**	**Notification CFR**
Meningococcal meningitis	172	0.18 (954)	0.04 (3918)
Meningococcal septicaemia	973	0.35 (2776)	0.38 (2581)
Streptococcus pnuemoniae	725	0.72 (1004)	0.60 (1217)
TOTAL	1870	0.4 (4734)	0.24 (7716)

4.4.2 Trends of number of lumbar punctures performed

The exercise to examine trends in LPs performed in the South West region of England derived data from 6 of 18 laboratories . A total of 35,671 (14,192 among 15+ year olds) CSF specimens were received by these labs, with a median of 271 CSFs (range 24 to 756) per laboratory per year. Due to the incompleteness of the available data, i.e. a number of CSFs received for analysis by the HPA (at the time PHLS) laboratories, (2 laboratories had data for the entire study period; 2 only from 1994 to 2000; and the other 2 had data from 1995 and 1996, respectively to 2000) it is appropriate to be cautious when drawing conclusions about the trends of LPs. Nevertheless, the number of CSF specimens received by the laboratories did increase year on year, from 2544 specimens in 1991 to 4115 specimens in 2000. The increase was steeper for adults, Poisson regression coefficient for adults was y=98 per year, compared to y=23 per year for children.

4.4.3 Conclusion

This study provides evidence that bacterial meningitis is an important public health problem in England & Wales insofar as much of the disease is vaccine preventable and it poses a large burden in terms of high fatality. This study shows that the epidemiology of bacterial meningitis is changing among adults in the England and Wales. Vaccination programmes in children and the re-emergence of TB appear to be making impacts in opposing directions.

The falling mortality rate is encouraging and suggests that standards of clinical management may be improving. Nonetheless, bacterial meningitis still results in considerable morbidity and mortality, and with the advances in the vaccine development, but also the potential changes in the causative bacteria, both, a detailed epidemiological monitoring and a high index of clinical suspicion for meningitis among adult patients should be maintained.

4.5 Discussion

An overall discussion of the findings is deferred till Chapter 8; here I will address specifically the limitations and strengths of this particular aspect of the study.

4.5.1 Limitations of the study

4.5.1.a Limitations of the data

The main limitation of this study was the completeness and the sensitivities of the reporting systems used. Under-reporting in routine surveillance systems is well recognised (Goldacre and Miller 1976; Davies 1989; MacLehose, Brand et al. 2001) so that reported incidence provide an underestimate of the true rates (see Chapter 5). The trends in the epidemiology of meningococcal disease observed may have been influenced by the introduction of non-culture diagnostic techniques during the study period, such as PCR testing (Ni, Knight et al. 1992). However, this trend has continued long after these techniques became introduced into routine use, i.e. changing to a decreasing trend only in the early 2000, probably due to the impact of Men C vaccination.

A reporting bias from variation in the use of diagnostic LPs, as reported from other studies (Ramsay, Kaczmarski et al. 1997; Wylie, Stevens et al. 1997), may have influenced the observed differences in trends for meningococcal meningitis and meningococcal septicaemia. However, I was unable to confirm a decreasing trend on LPs performed from the South West laboratory data. The observed differences in trends for meningococcal meningitis between laboratory and clinically notified data as well as the low fatality among those aged 85 years and older using clinical notified cases (as compared to cases reported by laboratory testing) may, also, be explained by differences if diagnostic practices, such as clinically recognising meningitis but not

examining the CSF, instead the testing / confirmation is done from the blood samples.

These data did not examine incidence by ethnicity, as the data was not available. Thus I was not able to demonstrate whether ethnic minorities are at higher risk of acquiring disease and of dying, as it has been reported in other studies (Rosenstein, Perkins et al. 1999). Despite these limitations, this data should be generalisable to the rest of the UK and to other European with similar population structures.

4.5.1.b Differences between the surveillance data

As noted in Chapter 3 the surveillance for CABM and MS is carried out by the clinical notification system (ONS) and the laboratory reports, by different causative organism. The source of reporting for both systems is different, i.e. clinicians for the ONS surveillance and microbiologists for the laboratory surveillance. These are both dependent on diagnostic practices and to some extent dependent on each other. Issues with reliability of data sources and the actual reporting, in particular following introduction of new surveillance systems or new public health initiatives (as it was the case during the period of my study with inrocduction of ESMD) has been reported (Olowokure, Hawker et al. 2000) (Freed, Green et al. 2008).The clinical notifications though are less sensitive for identifications of cases, whilst laboratory reports are less sensitive for identification of deaths. This was highlighted with the case-fatality rate estimates where the rates would exceed 100% in some occasions.
Realising the issues of underreporting with the routine data-sources and, as noted earlier, in order to improve the estimates of incidence and mortality form the routine surveillance data, I undertook a capture-recapture analysis, which is reported in the next Chapter (Chapter 5).

4.5.1.c Limitations with statistical methods

I have used Poisson Regression models, mostly, to calculate the incidence rates of the disease. There might be several limitations with this method, given the data used, and that because of the assumptions in Poisson Regression, mainly that:

1. The disease rate changes linearly on the log scale (and hence exponentially in terms of actual rates) with equal increment increases in the exposure variable – as with most infectious disease the disease is not usually linearly associated with exposure; there are complicated models of transmission, including host, environmental, and causative agent interactions, that determine whether one will get ill upon exposure or not. However, the Poisson regression framework provides a convenient empirical representation in which to test for exposure effects, without involving detailed modelling of processes on which data is seldom available.

2. At each level of the covariates the number of cases has variance equal to the mean - results suggesting that the data did not vary greatly from this assumption; and where there was some variation I have presented results from the Negative Binomial Regression models, rather then Poisson regression. These gave comparable results.

3. Observations are independent – only about 2% of cases of MD (meningitis and septicaemia) are linked, i.e. are dependent on other cases; and less so for meningitis caused by other causative agent. Therefore, the independence assumption is unlikely to be violated in any major way.

4.5.2 Strengths of this study

In Chapter 8 I will discuss in more detail the strengths of this study as well as the interpretation of the results in context of other published research; here I will briefly discuss the key strengths of this study.

This is the first study to examine the national (England and Wales) epidemiology of CABM and MS amongst adults. Around the same time a similar study was undertaken for Scotland, and most of the aspects of the epidemiology are similar (Kyaw, Christie et al. 2002). I will present a brief comparison between this and my study in the section below.

The interpretation of the results should be generalisable to other countries with a similar epidemiology, similar demographics, public health and surveillance systems.

I undertook comprehensive analysis, examining age, sex, time, regional epidemiology for the causative organisms.

The statistical analyses are robust; I employed appropriate methods and applied them robustly, compared and got reassuringly similar results between Poisson regression and NBreg models.

I presented results from both the available data sources, i.e. clinical notifications and laboratory reports, and discussed discrepancies (where they occurred) between the both.

4.5.2.a Comparing the two studies examining the epidemiology of bacterial meningitis: one in Scotland (Kyaw et al) and the other in England and Wales (my study)

Kyaw et al used laboratory reports of invasive meningococcal, pneumococcal, *Haemophilus influenzae*, Group B Streptococcus (GBS) and *Listeria monocytogenes*

isolates and examined the epidemiology of meningitis and invasive non-meningitic disease (INMD) caused by these 5 pathogens. They compared the data for two time periods, and that before (1983-91) and after (1992-99) the introduction of *the H. influenzae* type B conjugate vaccine (Hib) in the childhood immunisation programme in Scotland.

I used the laboratory reports, as well as clinical notifications for meningitis, based on the respective ICD 10 codes (see Data and Methods), for all CSF isolates of the seven pathogens (see Data and Methods) and the blood isolates for *N. meningitidis*.

I examined these data for the period 1991 to 2002. In this section I will compare the results by Kyaw et al for their second period of the study, ie 1992-99.

There were a few differences between the two studies, including:

1. The study population:
    a. The study by Kyaw et al (the Scottish study) examined the disease in all ages whilst I examined the adult population only (main results presented in Chapter 4 in this thesis).
    b. My study population was England and Wales, whilst Kyaw et al examined the disease in the population of Scotland.
2. The study period (as noted above) the Scottish study was between 1983 to 1999 whilst for my study was 1991 to 2001.
3. The Scottish study examined only 5 causative pathogens (as opposed to 7 in my study)
4. The disease examined – I only examined meningitis except for *N. meningitidis* for which I examined septicaemia as well (that is the only other form of invasive disease caused by *N. meningitidis*), whilst in the Scottish study the authors examined a wider range of invasive disease, including meningitis and

invasive non-meningitis disease (INMD), in most cases this includes septicaemia and pneumonia (eg due to HiB and *S. Pneumoniae* are amongst the more common ones, see Chapter 2 Background)

5. In the Scottish study *N. meningitidis* was the most common cause of meningitis, accounting for 47% of cases in 1992-99, whilst in my study, data for England and Wales, *S. pneumoniae* with 43.6% of meningitis cases was the most common cause, and *N.meningitidis* was the second most common cause of meningitis (CSF isolates) accounting for 33.5% of all CSF isolates.

The potential reasons for this difference are:

- I had a wider list of causative organisms of CABM, 7 as opposed to 5 in the Scottish study, hence a possible dilution of the overall proportion accountable to each organism, in this case *N. meningitidis*.
- I examined the data for a longer period, that is up to and including 2002 for difference from the Scottish study (up to 1999) therefore the impact of the Men C conjugate vaccine would have been reflected in my data but not in the Kyaw *et al* study..
- There seems to be a grater proportion of cases of suspected meningitis that are not diagnosed through the CSF (a lumbar puncture not performed) in England and Wales as compared to Scotland, and the proportion of meningitis cases caused by to *N. meningitidis* in the clinical notifications is grater than in the laboratory reports. Also, similar to the Scottish study, clinical notifications in m ysutdy did not show a decreasing trend for meningococcal meningitis (whilst this was significant in the laboratory reports).

6. A major difference in the findings was in the epidemiology of meningitis caused by HiB and that :

a. Hib was the second most common cause of meningitis in the Scottish study (31%), whilst in my study HiB was only accountable for 4.4% of cases of meningitis in the entire study period.

b. The incidence of HiB in the Scottish study remained unchanged in the adult population in the post-vaccination period (ie 1992 to 1999) whilst in my study I found a decreasing incidence.

The main explanations for these differences are:

c. *HiB* is a major cause of meningitis in childhood but not adulthood (and my study was restricted to adult population) therefore a grater proportion of cases is accountable to HiB in the overall population (all ages as opposed to adults only).

d. *Another potential explanation is that up to 1996* Hib vaccine was given as a separate injection, but in 1996 a combined DTP-Hib vaccine was introduced which has consequently shown to have a better effectiveness in long term immunity as well as heard immunity. Therefore as my study extended further beyond the 1996 cut-off (from single vaccine to vaccine containing whole cell pertusis) the impact of heard immunity was probably grater than up to 1999 (Heath and Ramsay 2003)

However, the most of the main findings between the two studies are similar, and these include:

1. In both studies a significant increasing incidence of meningococcal septicaemia is reported, in the Kyaw et al study it is referred to as invasive non-meningitis disease (INMD) caused by N. *meningitidis.*

1) In both studies a decreasing incidence of bacterial meningitis caused by *L. monocytogenes* is reported.

2) Also, similar to the Scottish study I found a significant decreasing incidence of meningitis caused by HiB in a non-vaccinating population (my study population is adults).

It is therefore, reassuring for my study that the majority of the main findings are similar between both studies, and my study provides additional evidence of the changing epidemiology of CABM and MS in England and Wales in similar directions with the studies in populations with a similar demographical background and context.

Chapter Five

Improving estimates of community acquired bacterial meningitis: an application of a capture-recapture analysis of pneumococcal meningitis in England

Chapter Five - Table of content

5.1 Introduction

> Not everything that can be counted counts, and not everything that counts can be counted!
>
> **A. Einstein**

Pneumococcal meningitis is one of the three most common forms of bacterial meningitis overall, and the most common form of meningitis amongst adults (Kragsbjerg, Kallman et al. 1994) (Urwin, Yuan et al. 1996; Weisfelt, van de Beek et al. 2006).

The uncertainty and the underreporting of infectious diseases in general, and meningitis in particular, are commonly acknowledged (MacLehose, McKee et al. 2002). The analysis of the routine surveillance data to examine the recent epidemiology of CABM and MS, which is presented in the previous chapter, further highlighted these concerns (see Chapter 4). The discrepancies between the routine sources that record the same conditions but from different sources, i.e. laboratory reports and clinical notifications, were apparent at many levels of analysis. For instance the regional analysis by gender seemed not to correspond with what was expected (data not shown); the case-fatality analysis in some instances produced estimates of over 100%.

These limitations prompted me to explore ways of measuring the underreporting in these routine data-sources, and of improving the estimates of bacterial meningitis incidence in England. Hence I undertook a capture-recapture analysis using the routine data sources for CABM and MS, including laboratory reports, clinical notifications / ONS death data, and Hospital Episode Statistics (HES).

I examined the surveillance of pneumococcal meningitis, one of the causative forms of CABM. I did not examine the surveillance for all forms of CABM as it would have been an impractical undertaking and because, for a correct application of the capture

recapture analysis, a well-defined condition is recommended, to ensure high specificity of the case definition. Hence, if I were to have included all forms of CABM, including those for which the case definition is less specific, the methodology would most likely have produced less reliable results. Meningococcal and pneumococcal meningitis, as seen in the previous Chapter, are the two most common forms of CABM amongst adults. At the time another researcher at the HPA / LSHTM, was undertaking a capture recapture study into meningococcal meningitis (Trotter). Therefore I decided to examine pneumococcal meningitis for the degree of under-ascertainment by the routine data-sources.

As showed in the previous Chapter, the routine data sources are useful in following trends of the disease and identifying changes in the occurrence of CABM and MS, for example those caused by outbreaks, or by changes in the underlying epidemiology. However, good estimates of incidence are needed to inform the population, clinicians and policy makers and to improve detection of disease. Planning of service provision and improvement of the clinical management, including early recognition of the disease and treatment, also requires accurate, reliable and timely epidemiological data. Policy making for prevention strategies, in this case vaccination policies are relevant, also requires accurate and reliable data on the burden of the disease.

I have measured the sensitivities of reporting of the incidence of and mortality (fatal Incidence, from now on I will refer to it as 'Mortality') from pneumococcal meningitis using a two-source capture-recapture analysis (PHLS RLR and HES for Incidence and HES and ONS data for Mortality) for each of the occurrences. I have calculated the case-fatality from the data yielded by the capture recapture and I have done simple costing calculations for the vaccination of the adult population. In this chapter I present a brief background to pneumococcal meningitis and the capture-recapture method, state the data and methods used, and describe the results of this work. At

the end I discuss the limitations and strengths of the research and its implications. This part of the research is published as peer-review article, reference:

Gjini, A., Stuart, J. M., et al. (2004). "Capture-recapture analysis and pneumococcal meningitis estimates in England." Emerg Infect Dis 10(1): 87-93.

5.2 Background

5.2.1 Clinical manifestation of pneumococcal infections

Streptococcus pneumoniae is a leading cause of pneumonia, bacteraemia, meningitis and otitis media in children and adults (Robbins 1978) (Weisfelt, van de Beek et al. 2006) (Boisier, Mainassara et al. 2007; Chanteau, Rose et al. 2007) (Melegaro, Edmunds et al. 2006). Pneumococcal infections occur at a number of different sites (e.g. upper and lower respiratory tract, cerebrospinal fluid) causing different disease manifestations. Pneumococcal infections can be divided into: i) invasive infections, such as: pneumonia, meningitis, and febrile bacteraemia; and ii) the non-invasive infections such as: otitis media, sinusitis, and bronchitis.

5.2.2 Epidemiology of pneumococcal meningitis

World-wide more than one million children die of pneumococcal disease every year, most of these being young children in developing countries (1999). In the developed world, including the UK, elderly persons carry the major disease burden. Long term effects of both invasive and non-invasive disease and the rapid emergence of drug resistant pneumococcus emphasize the need for effective public health prevention strategies.

Changes in the epidemiology of pneumococcal meningitis have been reported from most of the industrialized countries. For example a study during the 1990's in the Netherlands reported an increase in annual incidence from 1 to 1.5 per 100,000 between 1990 and 1996 (Spanjaard, van der Ende et al. 2000). An increased incidence, but also increased fatality amongst the elderly has been reported in the US (Butler and Schuchat 1999).

5.2.3 Public Health importance

Pneumococcal infections are spread from person to person by droplets, through coughing and sneezing, as is the case with most of the causative forms of CABM. It

is estimated that in the UK, respiratory infections account for 55% of all antibiotic prescriptions (Frischer, Heatlie et al. 2001). The emergence of pneumococci resistant to single or multiple antibiotics (Johnson, Speller et al. 1996; Cartwright 2002) and their association with outbreaks in child care centers and nursing homes underscores the urgent need for new preventive strategies (Nuorti, Butler et al. 1998).

Pneumococcal meningitis represents a small but important component of the total burden of pneumococcal disease, with a mortality of 25% and sequelae in excess of 50% of affected cases (Kragsbjerg, Kallman et al. 1994; Kornelisse, Westerbeek et al. 1995).

5.2.4 Prevention strategies

Some of these reports have noted that pneumococcal meningitis is now one of the most common forms of bacterial meningitis (Short and Tunkel 2000) and that it is predominantly a disease of adults, rather than of infants and children (Tsai, Griffin et al. 2008). These findings have led to suggestions that we need to change the management of bacterial meningitis (Short and Tunkel 2000).

There is an increasing public health emphasis on the prevention of pneumococcal meningitis and pneumococcal disease in general (Quick, Hoge et al. 1993; Schuchat, Robinson et al. 1997; Black, Shinefield et al. 2000). This follows the great success of prevention of two other common forms of CABM: HiB and Men C meningitis (see Chapter 2). There is compelling data to support the provision of pneumococcal conjugate vaccine for children (Sims, Steinmann et al. 1988) and considerable although arguably less robust evidence to support pneumococcal vaccination with polysaccharide vaccine in the elderly (Abeni, Brancato et al. 1994; 1995; Fedson 1999; MacLehose, McKee et al. 2002). If pneumococcal vaccination is to be introduced into the general adult population accurate estimates of the burden of invasive pneumococcal disease are needed.

5.2.5 Uncertainty of routine data sources

Geographical differences in the distribution of invasive pneumococcal disease may render small surveillance data-sets poorly generalisable and it is widely accepted that infectious diseases are commonly underreported (Reintjes, Termorshuizen et al. 1999). Population based surveys and active surveillance systems, the ideal methods for estimating prevalence and incidence of disease, are resource intensive. To overcome these problems, methods such as capture-recapture (Smith, Stuart et al. 1998) have been used effectively for both chronic disease and infectious disease epidemiology (Hook and Regal 1995; Faustini, Fano et al. 2000).

5.2.6 Capture recapture method

The capture-recapture method originated in fisheries and wildlife biology, and is widely used for assessing the abundance of wildlife populations. It is also commonly used in epidemiology and in various public health surveillance projects with aim of improving estimates of health occurrences (International Working Group for Disease Monitoring and Forecasting. 1995; International Working Group for Disease Monitoring and Forecasting). It has successfully been used in cancer epidemiology to improve the data that supports planning and provision of health services (Crocetti, Miccinesi et al. 2001). It has been identified as a useful tool in identifying different sub-groups in the surveillance populations, e.g. risk groups in patients with traumatic brain injury (Schootman, Harlan et al. 2000), and has found multiple use in infectious disease epidemiology (Reintjes, Termorshuizen et al. 1999) (Devine, Bellis et al. 1998; Tocque, Bellis et al. 2001) (Faustini, Fano et al. 2000), (Ferrer Evangelista, Ballester Diez et al. 1997); and has been widely used to estimate the population size of injecting drug users (Larson, Stevens et al. 1994; Hickman, Sutcliffe et al. 1999).

5.3 Methods

5.3.1 Data sources

HES and PHLS reconciled laboratory reports on pneumococcal disease (RLR) data for England were compared for the incidence analysis; and HES and ONS data for England were compared for the mortality analysis. HES were available only for hospitals in England; this prevented an analysis based on a larger UK data set. The details of these data sources and the data extracted for this research are given in Chapter 3.

5.3.2 Extraction of data

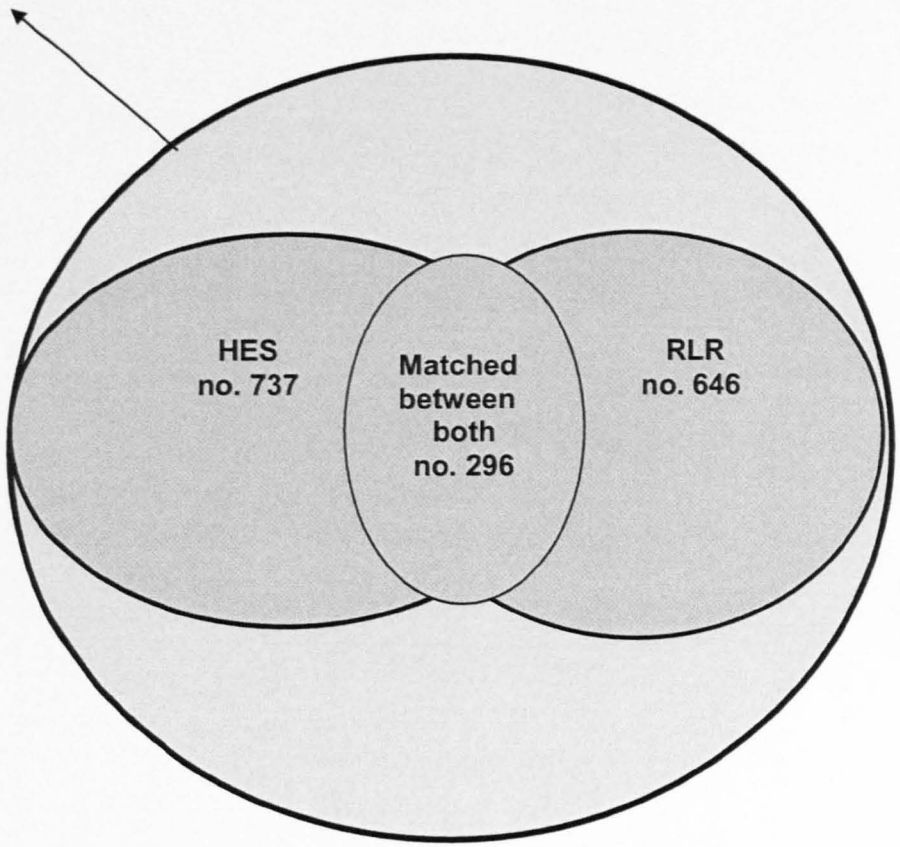
All adults in England 16 years and older with a diagnosis of pneumococcal meningitis were identified in HES and PHLS RLR for England for the incidence analysis, and HES and ONS for England for the mortality analysis. PHLS RLR data for the year 2000 were not available at the time of the study and the HES data was recorded as financial years 1996 – 1999. Therefore the incidence analysis was restricted to the period between April 1996 to December 1999. The mortality analysis was conducted using records from April 1996 to March 2000. For the case-fatality estimates, mortality analysis was restricted to December 1999, to be comparable with incidence analysis.

5.3.3 Validation of data sources

To validate the diagnosis and matching in the data extracts, consultant microbiologists in 17 laboratories providing clinical microbiology services to all acute hospital trusts in the South West Region of England were sent line listings of PHLS RLR and HES extracts relating to their laboratory and acute NHS Trust respectively. They then verified the correctness of diagnosis and matching according to their own laboratory, and they were able to use further personal identifiers. They also obtained

details from their local NHS Trust of hospital episode diagnoses of pneumococcal meningitis for cross checking against PHLS RLR and HES records.

Figure 5.1 - Diagram showing the number of records by the two data-sources, HES and RLR. The estimated true total number of cases in the population, calculated by the Hook and Regal method, based on the number of matched records identified between the two data-sources.



5.3.5 Matching and capture–recapture analysis

The capture-recapture method quantifies the degree of overlap between two or more sources to estimate the number of unobserved subjects by any source examined. Figure 4.1. The sensitivities of the data sources examined, was then estimated by using the number of cases yielded from the capture-recapture and the number of cases reported within each of the data sources. Further details of the capture-recapture method and the assumptions it makes are presented in Chapter 3.

5.3.5.a Sensitivity analysis

In order to test the validity and reliability of the method used, I performed a series of sensitivity analyses. I carried out the first sensitivity analysis using more or less stringent criteria for identification of duplicates, matching on the records using age and region instead of '*Date of birth*' and '*Hospital NHS Trusts*' as identifiers.

I also performed analysis based on all diagnostic fields, as opposed to the first diagnostic field for identifying the cases. The inclusion criteria for HES was all cases where pneumococcal meningitis (ICD 10: G001) was recorded in any of the diagnostic fields in the HES data-base, and not just the main diagnostic field. The rest of the criteria, including the selection of duplicates remained the same as for the main analysis.

5.3.6 Statistical analysis

For each source, the sensitivity of the reporting systems was calculated as the number of cases of pneumococcal meningitis reported to one source over the total number of cases estimated from the capture-recapture analysis. Case fatality percentages were calculated from the estimated total number of deaths and the estimated total number of cases in the population. The further details of statistical methods and analysis performed are presented in Chapter 3.

Table 5.1 Summary of data on Pneumococcal Meningitis cases.

Ages 16 years and older in England from the data sources used, Reconciled Laboratory Reports and Hospital Episode Statistics

	Year			Age group			Region			Sex			Death status	
	RLR (%)	**HES (%)**		**RLR (%)**	**HES (%)**		**RLR (%)**	**HES (%)**		**RLR (%)**	**HES (%)**		**RLR (%)**	**HES (%)**
1996/97	133 (20.6)	239 (32.4)	**16-19**	16 (2.5)	20 (2.7)	**NORTH & YORK**	85 (11.5)	62 (9.6)	**F**	301 (46.6)	353 (48.0)	**N**	42 (6.5)	597 (81)
1997/98	182 (28.1)	194 (26.3)	**20-24**	16 (2.5)	16 (2.2)	**TRENT**	77 (10.5)	77 (12)	**M**	336 (52)	382 (51.8)	**Y**	64 (10)	140 (19)
1998/99	151 (23.4)	190 (25.8)	**25-44**	145 (22.3)	175 (23.7)	**WEST MIDLANDS**	72 (9.7)	54 (8.3)	**NR**	9 (1.4)	2 (0.2)	**NR**	540 (83.6)	0
1999*	180 (27.9)	114 (15.5)	**45-64**	238 (36.9)	284 (38.5)	**NORTH WEST**	101 (13.7)	69 (10.7)						
			65-74	135 (21)	140 (19)	**EASTERN**	84 (11.4)	64 (10)						
			75-84	75 (11.6)	78 (10.6)	**LONDON**	117 (15.9)	183 (28.3)						
			85+	21 (0.15)	24 (3.2)	**SOUTH EAST**	113 (15.3)	47 (7.3)						
						SOUTH WEST	88 (11.9)	90 (13.9)						
Total	646	737		646	737		646	737		646	737		646	737

* Data not available for Jan- March 2000 NR= Not recorded

5.4 Results

5.4.1 Incidence

Between April 1996 and December 1999, 668 isolates of *S. pneumoniae* from patients with meningitis were documented in the RLR, and 1069 cases of pneumococcal meningitis were recorded in HES. After excluding multiple records (20 from RLR and 332 from HES) and 2 records from the RLR in which date of birth and age were missing, 646 records in RLR and 737 in HES were retained for analysis. The mean age of the cases in the RLR (55.8 years [range 16 – 97]) and HES data sources (55.3 years [range 16 – 96]) was similar, as was their sex distribution (52% were male).

Matching was achieved in only 296 of cases, demonstrating an overlap of less than half the records between the data sources. It was therefore estimated that an additional 521 (95% CI 477 to 568) cases were not captured by either source. The capture-recapture analysis thus revealed a total of 1608 (95% CI 1483 to 1747) cases of adult pneumococcal meningitis. The estimated sensitivities of the data collection systems for pneumococcal meningitis were therefore 40% (95% CI 37 to 44) for RLR and 46% (95% CI 42 to 50) for HES (Table 4.2). Sensitivity estimates varied by year of reporting, but no evidence of a trend was shown across the years (p-value 0.30 for RLR and 0.67 for HES) (Table 5.2) or the age-groups (Table 5.3). The lowest sensitivities were observed in those aged 85 or more (16% and 19% for RLR and HES, respectively) and the sensitivities of both data sources were significantly lower in those aged 85 or more compared to those aged 84 or under (p=0.002 and p=0.03 for RLR and HES, respectively; Table 5.3). Incidence rates using capture-recapture estimates decreased from 1.36/100,000 p.a. in 1996/97 to 0.78/100,000 p.a. in 1988/99.

Table 5.2 - Capture - recapture analysis for the number of cases of pneumococcal meningitis among adults (16 years and older) in England, April 1996 to December 1999, by time period

	Number of records in the data sources			Capture - recapture analysis			
Time Period	RLR*	HES**	Matched records	Unreported cases [95% CI]	Total number of cases in population [95% CI]	Sensitivity RLR% [95% CI]	Sensitivity HES% [95% CI]
Apr 1996 - Mar 1997	195	239	82	216 [156, 300]	568 [487, 668]	34 [28, 40]	42 [35, 49]
Apr 1997 -Mar 1998	168	194	70	174 [121, 248]	466 [393, 556]	36 [29, 43]	42 [34, 49]
Apr 1998 - Mar 1999	172	190	99	67 [46, 96]	330 [286, 379]	52 [45, 59]	58 [50, 65]
Apr 1999 - Dec 1999#	111	114	45	101 [64, 158]	281 [228, 350]	39 [31, 49]	40 [31, 50]
All study period April 1996 - Dec 1999	646	737	296	521 [434, 625]	1608 [1483, 1747]	40 [37, 44]	46 [42, 50]

** Reconciled Laboratory Reports; ** Hospital Episode Statistics ; # RLR Data not available for Jan – March 00*

Table 5.3 - Capture - recapture analysis for the number of cases of pneumococcal meningitis among adults (16 years and older) in England, April 1996 to December 1999, by age group

	Number of records in the data sources			Capture - recapture analysis			
Age group	**RLR**	**HES**	**Matched records**	**Unreported cases [95% CI]**	**Total number of cases in population [95% CI]**	**Sensitivity RLR % [95% CI]**	**Sensitivity HES % [95% CI]**
16 – 24	32	35	15	23 [9, 52]	75 [52, 110]	43 [26, 60]	47 [29, 65]
25 - 44	145	175	64	140 [96, 205]	396 [333, 476]	37 [29, 44]	44 [36, 52]
45 - 64	238	284	126	140 [103, 188]	536 [474, 607]	44 [39, 50]	53 [47, 59]
65 - 74	135	140	57	114 [75, 170]	332 [276, 402]	41 [33, 49]	42 [34, 51]
75 - 84	75	78	30	72 [41, 125]	195 [151, 257]	38 [28, 49]	40 [29, 51]
85+*	21	25	4	89 [-]	131 [-]	16 [-]	19 [-]

*due to small numbers in the matching records cell, it was not possible to calculate reliable CIs for this age group (calculations yielding an infinite upper limit).

Matched cases did not vary significantly from unmatched cases, when examined by age, by gender or by year. The mean difference between the specimen date (RLR) and date of episode (HES) for the matched cases was 0.14 days (range -10 to 24), with 70% of cases having the same date recorded in both data sources. Information on other covariates was largely consistent within the matched records.

5.4.2 Mortality

Between April 1996 to March 2000, 197 deaths from pneumococcal meningitis in England were reported by ONS, whereas 195 deaths were recorded in HES. The mean age of the cases in the ONS (61.7 years [range 16 – 96]) and HES data sources (62.7 years [range 16 – 97]) was similar, as was their sex distribution (50% were male).

Between the two data set 95 cases were matched. Capture-recapture matching analysis revealed 107 (95% CI 75 to 150) adult deaths from pneumococcal meningitis not reported by either source, resulting in an estimated total of 404 (95% CI 350 to 466) deaths . The estimated sensitivity of the ONS and HES data collection systems for death from pneumococcal meningitis was 49% (95% CI 42 to 56) and 48% (95%CI 41 to 55), respectively. There was a significant decrease in the ascertainment of deaths over the years for HES but not for ONS (test-for-trend p=0.03 and p=0.51, respectively). Mortality rates, similarly to incidence, decreased over the study years from 0.30 to 0.15/100,000 p.a, hence the case-fatality rate did not change. The data from the capture–recapture analysis yields an estimated case-fatality rate for pneumococcal meningitis of 24% (95% CI 21% to 26%) (Table 4.4). The case-fatality rates were calculated by dividing the number of deaths and number of cases derived from the capture-recapture analysis, in Excel .

Table 5.4 - Capture - recapture analysis for the number of deaths from pneumococcal meningitis among adults (16 years and older) in England, April 1996 to March 2000, by time period

	Number of records in the data sources			Capture - recapture analysis				
Time Period	**ONS**	**HES**	**Matched records**	**Unreported deaths [95% CI]**	**Total number of deaths in population [95% CI]**	**Sensitivity ONS % [95% CI]**	**Sensitivity HES % [95% CI]**	**Case Fatality %* [95% CI]**
Apr 1996 – Mar 1997	65	55	28	36 [18, 66]	128 [98, 167]	51 [38, 64]	43 [31, 55]	23 [19, 27]
Apr 1997 - Mar 1998	51	57	20	57 [30, 113]	145 [106, 208]	35 [23, 48]	40 [26, 53]	31 [26, 37]
Apr 1998 – Mar 1999	44	45	25	15 [7, 31]	79 [59, 104]	56 [41, 70]	57 [42, 71]	24 [19, 31]
Apr 1999 – Mar 2000	37	38	22	11 [4, 24]	64 [46, 85]	58 [42, 74]	58 [43, 75]	12 [9, 18] ^
All study period April 1996 – March 2000	197	195	95	107 [75, 150]	404 [350, 466]	49 [42, 56]	48 [41, 55]	24 [21, 26]^

** Based on the number of cases in Table 1.*

^ Excluding deaths between Jan `00 – Mar `00 so to be comparable with the number of cases in Table 1

5.4.3 Sensitivity analysis of the incidence data

Using less stringent criteria for identification of duplicates

Application of less stringent criteria, matching on 'Age' instead of 'Date of birth', yielded an additional 13 matched records. This gave an estimate for the total number of cases in the population of 1541 cases, yielding a sensitivity of 42% for HES and 48% for RLR. Application of more stringent matching criteria including matching on region resulted in an increased estimated number of cases from 1608 to 2061, giving a sensitivity for HES and RLR of 31.3% and 35.8%, respectively.

Using all diagnostic fields for identification of cases in HES data

Extracting the data from HES for subjects with a diagnosis of pneumococcal meningitis (ICD 10 G001) in any diagnostic field, identified an additional 76 records compared to the data extracted for the 1st diagnostic field only as in the main analysis.

Matching HES and RLR data-sources identified a total of 318 matches (22 extra matches compared to the main analysis), giving an estimated total of 1652 cases in the population, and sensitivities of the surveillance systems as 49.2% and 39.1% for HES and RLR, respectively (Table 5.5).

Table 5.5 - Sensitivity analysis for the capture-recapture method all vs 1st diagnostic field.

	Total records in the data sources		Results of capture - recapture analysis				
1996 -1999	RLR	HES	Matched records	Unreported cases	Total cases in population	Sensitivity RLR %	Sensitivity HES %
HES all Dg fields	646	813	318	511	1652	39.1	49.2
HES 1st Dg field, only	646	737	296	521	1608	40.2	45.8

5.4.4 Validation of data sources using local regional data

For protecting the cofidentiality of patients, the data is not available for research purposes with identified names of individuals. However the local laboratories and hospitals do possess and have access to such data for their quality assurance purposes. Hence I asked all the HPA (at the time PHLS) laboratries (17) in the South West region of England to identify from their records the data I possessed and check by using further personal identifiers, i.e. names, along with DoB and other identifiers to match against hospital recods. Data were validated in 13 of the 17 laboratories approached, covering 76 (88%) of the 86 RLR records and 75 (86%) of the 87 HES records identified in the South West Region of England. 38 cases matched between the sources, yielding an estimated capture-recapture total of 150.

Of the 38 original matches, 37 were confirmed as correct from laboratory records. Two additional matches were identified (one incorrect date of birth in HES, one in RLR). Of the remaining 35 records in HES but not in RLR, 17 had no laboratory record, 9 had laboratory evidence of pneumococcal meningitis, 8 had positive blood cultures for *Streptococcus pneumoniae*, and 1 had been incorrectly reported (meningitis due to Group B streptococci). Of the 36 records in RLR but not in HES, 33 had positive CSF cultures for *S. pneumoniae*, 1 only had septic arthritis, and 2 had no laboratory record. An additional 5 cases were identified (3 only in laboratory records and 2 only in hospital trust records) that were not in the main study. Taking account of the 2 additional matches, the 2 incorrect diagnoses and the 5 additional cases, the capture-recapture estimate for the South West Region was unchanged at 150 cases.

5.5 Discussion

5.5.1 Strengths and limitations

Although the use of capture-recapture analysis to estimate the burden of disease has its drawbacks (Tilling 2001), in the absence of large population base surveys, this method can provide good estimates of disease incidence and associated deaths (Hickman, Cox et al. 1999) (Brenner 1995), or at least more realistic estimates than those based on single databases. This study of adult pneumococcal meningitis has made several assumptions relating to the data and its analysis which must first be considered before these estimates can be used in policy making nationally and elsewhere.

Data sources

I used the three national data sources (NOTE analysis for each, incidence and mortality, was based in a two-source analysis), which are assumed to be the most representative and complete for pneumococcal meningitis. The data was accumulated in each of the data sources used in parallel and in a non-selective manner. Based on the premise that the population did not change significantly within the study period [ONS population data], I assume that the population under study varied similarly across sources . I was not able to include the clinician notification data in the incidence analysis because of the lack of personal identifiers and a date of infection.

Independence of sources

The assumption that sources are independent is rarely fully met in epidemiology (Hook and Regal 1995). It is likely that there is some positive dependence between the sources, in that the laboratory confirmation of a case (RLR) is likely to lead to a notification to HES and, if death occurs, notification to ONS. This dependence would have, if anything, lead to an underestimation of the total burden of disease (Brenner

1994) (Brenner 1995), as the number of matched cases is likely to be higher than it would have been under independence and therefore the estimated total population would have been smaller.

As I used a two-source capture-recapture method it was not possible to quantify this possible dependency of sources. A third representative and comparable source would have possibly been the clinical notifications to ONS, but: 1) due to the lack of personal identifiers it was not possible to include it in the analysis; and 2) the clinical notifications would probably be supplementary (i.e. a strong positive dependence, meaning a laboratory report would lead to a clinical notification) source to the lab reports, therefore the estimates yielded would be poorer, e.g. the 95% CI Of the estimates would be a lot wider due to the dependency (Chang, LaPorte et al. 1999).

It is highly unlikely that there is any negative dependency (ascertainment in one data source leading to non-ascertainment in the other) between sources which would have lead to an overestimation of the total population of pneumococcal meningitis cases and deaths (Brenner 1995).

The temporal trends

The estimated decreasing incidence during the study period could be suspected to have impact on the validity of the capture-recapture method. It would have been better accounted for if I did a loglinear model for timetrends. However, the data presented in Table 5.2 showing the analysis stratified by time, the overall estimate of the number of unrecorded cases is 521 and adding up the estimates of unrecorded cases for the 4 periods, we get a total of 558. This is the best estimate of the unrecorded cases, after allowing for time trends, which is a only very slightly different total number estimated. Temporal trends are often found in the studies measuring a condition by capture-recapture methods (Hook and Regal. 2000). Possible explanations for the decreasing incidence over the time may be found in the changes in diagnostic practices. It is hypothesized form the studies on meningococcal disease

that the decrease in CSF diagnostic samples is replaced with increased blood culture samples (Ramsay, Kaczmarski et al. 1997). Nonetheless, even if the validity of the capture-recapture method is not affected, still these diagnostic mis-practices do have an influence on the management of cases (Fuglsang-Damgaard, Pedersen et al. 2008), therefore better epidemiologic data, such as this study provides should help to improving the training and clinical practice.

Changes in surveillance systems

In 1996 the surveillance of Invasive Pneumococcal Disease (IPD) in England and Wales was enhanced by actively asking all labs to report IPD episodes and refer isolates for typing. This study covers the period from the beginning when the enhanced surveillance for IPD was introduced in England and Wales. A peak on reporting of blood isolates occurred in 1997 (probably when the changes in the surveillance achieved the highest impact) (George and Melegaro 2001). But, an increased reporting is not seen in this surveillance system for the CSF isolates. A similar divergent trend between meningitis and septicaemia has been observed with enhanced surveillance of meningococcal disease in the UK. These changes did not appear to affect the analysis, in as much as the estimates follow the trend of the routine data sources, nationally and internationally.

Equal probability of capture-recapture

I assumed that the probability of cases being captured by each source is not influenced by the characteristics of the case and that almost all cases recorded by the RLR and ONS were also hospitalised. As shown in Table 5.1 cases derived from the data sources were similar in terms of age, gender and outcome. Recaptured cases did not vary significantly from cases not recaptured, when examined by gender, by year, or age with exception of the older age group, 85+ (Table 5.3), though this did not have a major impact on the estimates. This is seen if we add up the total number of unreported cases by age group in Table 5.3, we get 578,

compared to 521 cases from the overall analysis. The discrepancy is due to the fact that the capture probability does vary with age, and is lower in 85+. However, the the overall impact on estimates of total burden is not huge, probably boosting the total number of unrecorded cases by only about 10% probably, which in the overall estimates of the total population would have hada negligible impact towards an underestimate. Nonetheless, the public health message is important: diagnostic practice for 85+ year olds is worse. This suggests that cases captured in the either source had an equal probability to be matched between the two data sources because of their characteristics, except for the older people (Cormack 1999).

Misclassification of diagnosis

It is possible that there was some diagnostic misclassification of pneumococcal meningitis during the recording of the HES and the ONS data (2000; Williams JG 2002). However, it would seem more likely that misclassification of pneumococcal meningitis onto meningitis cause 'unspecified' or cause 'unknown' occurred; most likely because of missing laboratory confirmation. This misclassification, if occurring, is likely to be similar across the two data sources examined, i.e. lab-reports / HES / ONS deaths. However, even if misclassification occurs capture-recapture analysis normally provides more reliable estimates than routine surveillance systems (Brenner 1996).

I restricted the analysis to records of pneumococcal meningitis from the primary diagnosis field of HES records, to avoid diagnoses not related to the reason for hospitalisation. As meningitis is commonly a serious condition, it is normally recorded as primary diagnosis in the first diagnostic field. It is unusual for meningitis to be recorded in the other diagnostic fields where typically chronic diseases are recorded. Searching other diagnostic fields in the South-West region validation analysis did not identify any additional cases. The sensitivity analysis using all diagnostic fields in the matching process did not reveal materially different results. The results from the main

analysis are likely to more reliable, as entries in other diagnostic fields may reflect past rather than current diagnosis.

Accuracy of diagnosis and matching

The study matching strategy was supported by the validation study conducted in the South West Region. This showed that matching without names for these data sources had a high degree of accuracy. An acceptable level of accuracy of recording laboratory confirmed cases was also found in both PHLS RLR and HES data sources, with only two false positive diagnoses being identified. There was no big change in the capture-recapture estimate after validation.

Meningitis represents about ten percent of invasive pneumococcal disease among adults (Laurichesse, Romaszko et al. 2001). If all invasive *pneumococcal* positive isolates from the HPA RLR had been included, this would have greatly increased the probability of including false cases in RLR, thus increasing the probability of false matches, leading to overestimated results of the matched cases, but an underestimate of the total number of cases in the population.

The inclusion of "non-specified meningitis" (ICD 10=G00.9) would have led to a similar increase in the probability of including false cases in HES, and a similar overestimate of the total number of cases.

Statistical analysis

The parametric bootstrapping method is not the best for calculating the confidence intervals for cells with small numbers as it sometimes produces unbounded results. However, this does not invalidate the method, it just reflects the uncertainty around the data. In such circumstances other methods, such as for example Cormack's approximate method (a profile likelihood method), provide an alternative. However I did not have the capacity to apply such methods. Nevertheless, problems of low counts only emerged in sub-analyses. The evaluation of incidence overall involved

sufficient numbers of cases that such problems did not arise. Several sensitivity analyses showed that the estimates and CIs were robust.

Another weakness of the analysis is not the calculation of CIs for the elderly. This could have been done using a full regression analysis allowing for time trends, age groups, sex. However, the results of my analysis show that such adjustments would have had a minor effect on the estimates, boosting the total number of unrecorded cases by only about 10% (see above under '*Equal probability of capture-recapture*'), hence with a negligible impact on the overall counts. (International Working Group for Disease Monitoring and Forecasting 1995)

Chapter Six

A review of hospital management of community acquired bacterial meningitis and meningococcal septicaemia in adults

Chapter Six - Table of content

6.1 Introduction and Background

In Chapter 4 I presented the epidemiologic burden of Bacterial meningitis and meningococcal septicaemia in adults in England and Wales, including the incidence and mortality rates; and in Chapter 5 I showed that these rates as estimated from the routine data sources, are in reality probably almost twice as high. Clinically these conditions are serious, indeed potentially devastating. They are more common in small children and teenagers; but their severity and fatality rates are just as high in adults, and even higher in the elderly.

A detailed description of the pathology, clinical presentation, recommended management of CABM and MS has been given in Chapter 2.

In children, the last decade has seen many advances in the control and management of these conditions. The very successful immunisation programmes for Hib and Men C have dramatically decreased the incidence of meningitis (Ramsay, Andrews et al. 2003), (McVernon, Ramsay et al. 2008) also there have been advances in clinical practice, reporting a reduced mortality and prevalence of long-term sequelae (Thorburn, Baines et al. 2001). In 2001 a study in clinical management of children highlighted improvements in the outcome of the disease (Booy, Habibi et al. 2001).

However, mortality amongst young adults has remained higher than amongst children. In June 1999 the British Infection Society (BIS) published the Guidelines for management of bacterial meningitis amongst adults (Begg. 1999). These guidelines were published in the BIS journal and recommended by the Chief Medical Officer for England. A national study reviewing the clinical management of meningococcal disease (MD) in children and young adults was undertaken in 2001 – 2. The preliminary reports from this study were concerning, reporting considerable deficiencies in the delivery of the health care to adult cases (Ninis, Phillips et al. 2005).

It was with this background that the Department of Health (DH) funded a proposal to review the clinical management of CABM and MS in adults in England and Wales. I was the Research Fellow on this project, and developed the study as follows.

I undertook a retrospective review of clinical management of adult cases at hospitals across England and Wales. I reviewed case-notes (including: Accident and & Emergency, medical and nursing) of patients admitted in the randomly selected hospitals and assessed the practices against the indicators and standards of clinical practice, which I had developed, based on the published BIS guidelines (Chapter 3).

This chapter presents the results of this research, which was a national review of the hospital management of adults with CABM and MS. Following this introduction I give a brief description of the methods used, a detailed description of the data and methods was presented in Chapter 3. Then I present the results, including the results of the pilot study that I undertook before embarking into the main study; then follow the results of the main study. At the end I discuss briefly the main findings in context; strengths and limitations of the study. A more detailed discussion and policy implications of the findings of this research are presented in Chapter 9.

This research has been published as a peer-reviewed article: Gjini, A. B., Stuart, J.M. *et al.* (2006). "Quality of in-hospital care for adults with acute bacterial meningitis: a national retrospective survey." Quarterly Journal of Medicine; 99(11): 761-9.

6.2 Data and methods

The detailed description of the Data and Methods used is given in Chapter 3. Here I will just recall them briefly.

This study was a retrospective review of case notes of patients with CABM and MS admitted and managed at a sample of randomly selected NHS hospital trusts in England and Wales between January 2000 and December 2001.

6.2.1 The pilot study

Prior to finalising the design of the main study, I undertook a pilot study with the aim of testing the reliability, validity of the study instrument (the questionnaire for data collection) and the feasibility of conducting the national review. The findings and the experience from the pilot study were fed into the design of the main study. Results are presented as plain percentages.

6.2.2 The main study - design and data collection

This was a national study reviewing the clinical management of CABM and MS amongst adults in England and Wales.

The study was designed and conducted as a retrospective review of case notes of patients admitted at the randomly selected hospitals.

The data was collected using a standardized case report form, which was revised following a pilot study in four hospital trusts.

6.2.2.1 Selection of hospitals

The primary sampling unit was the NHS healthcare trust. NHS hospital trusts were randomly selected from the list of all NHS hospital trusts across England and Wales. Two trusts were randomly selected from each of nine regions: the eight NHS regions of England (as in 2000/2001) and the single region of Wales. In trusts with more than one acute hospital, one hospital was randomly selected.

6.2.2.2 Cases of bacterial meningitis and meningococcal septicaemia

I reviewed the medical records of patients aged 16 years and older with a diagnosis of acute bacterial meningitis and/or meningococcal septicaemia presenting to 18 acute NHS healthcare trusts in England and Wales, between 1 January 2000 and 31 December 2001. Cases were identified by discharge diagnoses with ICD 10 codes.

6.2.2.3 Assessment of clinical practice, disease severity and outcome

As mentioned above, in the Background section of this chapter, standards of clinical practice were agreed by the expert panel convened for the study, based on the published BIS guidelines and the results of the plot study (see Appendix 3). These standards relate to multiple steps in the diagnosis and management process, as described in Chapter 2, Background. They provide an analysis framework for the study (Chapter 3, Figure 3.2)

6.2.3 Record keeping

The quality of data recording in the clinical notes was classified as: 'Good' if more than 75% of essential information (as specified in the Standards and Indicators, Appendix 3.) was recorded; 'Medium' if 50–75% was recorded and 'Poor' if less then 50% of essential information was recorded.

6.2.4 Outcome

The outcome of a case of CABM and MS was assessed using the following endpoints: death, length of hospital stay, and long-term sequelae (deafness, neurological deficit, major skin lesions or amputation).

6.2.5 Statistical analysis

I assessed the clinical practice based on the Standards and Indicators (Appendix 3.), adjusted to allow for:

- the clustering of the sample within hospitals and the within hospital correlation, as well as
- stratification by regions

wherever it was possible. If allowing for clustering effect resulted in increased the SE, of the estimate (e.g. proportion of cases) then results with this adjustment are presented.

6.3 The pilot study results

Four hospitals were included in the pilot study, one university teaching hospital and three district hospitals. The total number of records (cases of meningitis and/or meningococcal septicaemia) examined was 48. Numbers of records examined in the teaching hospital was 6 (12%) and in the district hospitals 15 (29%), 12 (25%) and 15 (31%) each.

6.3.1 Reliability and validity of the study instrument

The questionnaire was not difficult to use. Items in the questionnaire could easily relate to the information on the case notes. For items in which the information is not commonly recorded if the procedure is not done, it was not possible to differentiate between Not done and Not known.

6.3.2 Demographics of cases reviewed

Of the 48 cases reviewed 26 (54%) were female. Most cases were in the 45 to 64 age group (29%) whilst the elderly were the smallest proportions (i.e. 65+, 21%). See table 6.1.

Table 6.1 - Age distribution of cases reviewed in the pilot study.

Age group	Freq	Percent (%)
16-24yrs	11	23
25-44yrs	13	27
45-64yrs	14	29
65+ yrs	10	21
Total	48	100

6.3.3 Note recording

The standard of record keeping in the medical notes was as follows: 7 (15%) of the 48 case notes reviewed in the pilot study were classified as good (>= 75% of essential information recorded), 33 (68%) medium (50-75%) and 8 (17%) poor.

6.3.4 Management of cases at hospital

25 (51%) of the cases were managed initially in Accident and Emergency Departments of the NHS hospital trusts, and others were admitted straight to the wards. Most of the cases, 30 (62%) were managed in more than one department during their stay. 42 (88%) cases were managed in medical ward, 2 (4%) in infectious diseases wards, 3 (6%) in paediatric wards, and 19 (40%) in HDU/ICU.

6.3.5 Clinical management

6.3.5.1 Pre-Hospital management

32 out of 37 (86%) cases where information available, were seen by the GP before admission to hospital. In 5 of 26 (19%) where information recorded, there was evidence for GP having observed rash. Table 6.2, below, presents further information on pre-hospital management.

Table 6.2 - Pre-hospital management of cases of meningitis / septicaemia as recorded in the medical notes.

Pre-hospital management	Info recorded (%*)	Yes (%**)
Seen by GP before admission	37 (77)	32 (86.5)
GP observed rash	26 (54.2)	5 (19.2)
GP suspected dg	20 (41.6)	6 (30)
GP administered B Penicillin	1 (2.1)	1 (100)
**denominator is the total number of study records (no.48)*		
***denominator is the number of study records with info recorded*		

#among cases in which diagnoses was suspected.

In 6 of 20 records where information was available (30%) there was a record of GP diagnosing meningitis / meningococcal septicaemia. Among these 6 cases, Benzyl Penicillin was administered in only one, whereas in 5 cases (83%) it was not. In the 32 cases seen by a GP, irrespective of a GP diagnosis, Benzyl Penicillin was administered in only 2 cases.

6.3.5.2 Initial hospital management

Severely ill patients

25 of 40 (62%) cases where it was a recorded had neck stiffness present. 22 of 25 (88%) having a stiffed neck were managed at ICU. 13 of 41 (32%) where it was recorded, had a rash and 7 of these 13 (54%) were managed at ICU. 36 of the 48 cases (75%) had a GCS recorded. 6 of 7 cases with conscious level of GCS <=8 were managed at ICU.

3 of 29 (10%) cases in which neurological examination was recorded, had focal neurological signs. In 22 of 38 (58%) meningitis cases (the other 10 were

septicaemia), a neurologic examination was recorded to have had been done. Table 6.3 sets out key indicators for clinical management as recorded in medical notes.

Table 6.3 - Initial hospital management of cases of meningitis / septicaemia as recorded in the clinical notes.

Initial hospital management	Info recorded (%)	Performed Yes (%*)
Parenteral a.b. within 1hr	30 (62)	24 (80)
Differential diagnosis included meningitis / septicaemia	35 (73)	24 (69)
Parenteral a.b. throughout treatment course	39 (80)	31 (79)
Consultant visited within 24hrs	16 (33)	15 (94)
Lumbar Puncture done	44 (92)	27 (61)
CT before LP	25 (52)	17 (68)
Was CCDC contacted	26 (54)	21 (81)
Was CCDC contacted within 12hrs	12 (25)	6 (50)

* of cases for which information was available.

Lumbar Puncture (LP)

In 27 of 48 cases (56%) it was recorded that a LP had been performed. 17 of 27 cases where a LP was performed, had a Computerised Tomography (CT) before LP, and 5 cases not; while for 5 cases the information was missing. 6 cases had a record of not having a raised ICP. In 21 of 38 (55%) meningitis cases it was recorded that an LP had been performed. 2 of 3 cases in which papilloedema was recorded as present, had a CT scan performed. In 24 (69%) of 35 cases for which information was available, differential diagnosis included meningitis / meningococcal septicaemia at admission (<6hrs).

6.3.5.3 Other diagnostic investigation

Table 6.4 presents the information on the diagnostic investigations as recorded in the clinical notes.

Table 6.4 - Diagnostic investigations recorded.

Investigations	Recorded as done (%)
Urea	34/48 (79)
Blood Sugar	34/48 (79)
Chest X Ray	15/48 (31)
PO2	14/48 (29)
PCO2	14/48 (29)
PCO3	7/48 (15)
Clotting screen	32/48 (67)
Platelet count	40/48 (84)
Blood for Men. Culture	33/48 (69)
Blood Men PCR	11/48 (23)
CSF Men PCR	1/21 (4.8)
CSF Men Culture	14/21 (66)
Throat swab	10/48 (21)

*Including cases treated with Ceftriaxone as well.

Treatment

Where diagnosis was made at admission, in 15 of 19 cases parenteral antibiotics were administered within 1hr. In 31 of 39 cases intravenous antibiotics were administered throughout the treatment course. In 15 of 16 cases were information was recorded, a consultant visited the patient within the first 24hrs. 24 of 48 cases

received parenteral antibiotics within 1hour of arrival at hospital. (Although exact time was missing in some cases, I made an assessment, based on other information available, on the approximate time between admission and antibiotic administration).

6.3.6 Clinical outcomes

6.3.6.1 Final diagnosis

27 (56%) cases were diagnosed as meningitis alone,10 (21%) as meningococcal septicaemia alone, and 11(23%) cases were diagnosed as meningitis and meningococcal septicaemia. The organisms involved are listed in Table 6.5.

Table 6.5 - Causative organisms of meningitis cases

Organism	Number	Percent (%)
Haemophilus B Influenzae	1	2
Mycobacterium tuberculosis	1	2
Neisseria meningitidis Unidentified	5	10
Neisseria meningitidis B	2	4
Neisseria meningitidis C	3	6
Streptococcus pneumoniae	10	21
No isolate	16	33
Septicaemia, only	10	21
Total	48	100

6.3.6.2 Deaths

There were 4 deaths recorded before discharge from hospital (9%). Among the 15 cases managed at ICU there was 1 death (7%).

6.3.6.3 Sequelae

Information on sequelae recognised before discharge and/or at follow up was as follows: 7 cases had Deafness recorded at discharge, 6 Neurological deficit, and 10 cases had records for Other sequelae (these included: loss of sight, confusion, headache, loss of memory, intermittent tiredness, depression, diplopia, arthritis).

6.3.7 Notification and prophylaxis

In 21 cases it was recorded that the CCDC was contacted, and only in 6 cases was it recorded that the CCDC was contacted within 12 hours of diagnosis.

6.3.8 Recommendations for the main study

Based on the findings and the experience from this pilot study the following recommendations were made for the design and the conduct of the main study, including design of the study questionnaire and standards and indicators:

6.3.8.1 Standards to be used for assessment of management

The following indicators should be used to assess the standards of care:

- Mean time of referral from admission to ICU for severely ill patients.
- % of all bacterial meningitis and meningococcal septicaemia cases assessed by an ICU team during their hospitalisation.
- % of differential diagnoses that include meningitis / meningococcal septicaemia at *first assessment (<=12 hrs).*
- % of cases reported to CCDC on the day of admission, where MD diagnosis suspected.

6.3.8.2 Review of the study instrument

The following recommendations were set out for the study instrument (case report form, Appendix 5) and specifically relate to:

Item 5 Sequelae: to collect information whether recognised at discharge or at outpatient follow up. And to add a section to this item : 'Was a hearing test done? If yes, when (date). Result.

Items 8, 9 and 10: Information on investigations requested to be accompanied with whether investigations performed. If Yes should record the result of the investigation.

Add a new item to the study intrument: "Was the patient assessed by ICU team?"

Also, add a new item on: "Existing pre-medical conditions (chronic heart, lung, liver, renal diseases)."

6.3.9 Conclusion from the pilot study

The experience from the pilot study was useful for the design and conduct of the main study to review the clinical management of adults with CABM and MS in England and Wales.

Valuable information was obtained on the feasibility of the enrolment of hospital trusts and the cases; on the feasibility of data collection; on the validity, reliability and usefulness of the study questionnaire; and on key information about the recommended standards of practice on which to base indicators for assessing clinical management.

I reported on the experience and findings from the pilot study to the expert panel that was overseeing the review of hospital management study. As mentioned above I took account of and incorporated the recommendations that came out of the review from the expert panel into the design and conduct of the main study, which is presented below.

6.4 The main study

6.4.1 Characteristics of the patient population and NHS trusts

The sampling method has been described in Chapter 3 (give precise ref). Eighteen Acute NHS Hospital Trusts across England and Wales were included in the study. Of these, 3 were university teaching hospitals. These hospitals accounted for 23% (43 cases) of all cases included in the anlaysis for this study.

The median number of beds per hospital trust was 600 (i.q.r 375 to 650). All hospital trusts had an ICU; while 25% (5/19) had, also, an infectious disease unit. All the medical records reviewed and included in the analysis had been coded correctly and no apparent alternative diagnoses were documented in any of the records.

Within the 18 sampled hospitals, I identified a total of 212 cases that were diagnosed as bacterial meningitis or meningococcal septicaemia (ICD 10: A39; G00) in adults. For 5 cases their case notes were not available at the time of review, so were not included in the study. I also excluded 17 cases following study exclusion criteria, and that listing: 6 for past neurosurgery, 5 as immunocompromised (steroids, chemotherapy, HIV, splenectomia), and in 2 cases meningitis occurred more than 2 weeks after being admitted to hospital, 4 were referred from another hospital. The highest number of cases excluded from one trust was 4. Thus, a total 190 cases was included in the analysis.

Of these, 153 (81%) were recorded as having a diagnosis of suspected meningitis or septicaemia (and all of these would then contiue to have this as a final diagnosis, as otherwise they would have had been exclude from the study, see case definition, Chapter 3). Of the 190 cases; 107 (56%) had a recorded diagnosis of meningitis alone, 46 (24%) had a diagnosis of combined meningitis and septicaemia, and 37 (20%) of them of them the diagnosis recorded was of solely septicaemia.

The median number of cases enrolled in the study per trust was 8 cases (ranging between 4 and 16 cases from each hospital). The highest proportion of cases that one trust accounted for in the total number of cases in the study was 9% and the lowest 2%.

Table 6.6 - sets out the organisms involved and the main characteristics of the patients in the study cohort.

				Unweighted n (%)		Weighted[1] n (%)	
Age group	16 - 24			71	(37)	69	(37)
	25 - 64			87	(46)	87	(46)
	65+			32	(17)	34	(18)
Sex	female			94	(49)	98	(52)
	male			96	(51)	92	(48)
Co-morbidity[2]	No			165	(87)	164	(86)
	Yes			25	(13)	26	(14)
Diagnosis	*N. meningitidis*	serogroup B	26			30	
		serogroup C	9			9	
		serogroup Y	0			0	
		serogroup not recorded	25			24	
		total		60	(32)	63	(33)
	S. pneumoniae			25	(13)	27	(14)
	other			3	(2)	3	(1)
	clinical diagnosis alone*			102	(54)	98	(52)
Total				190	(100)	190	100

[1] = see methods

[2] = chronic heart, lung, kidney or liver disease

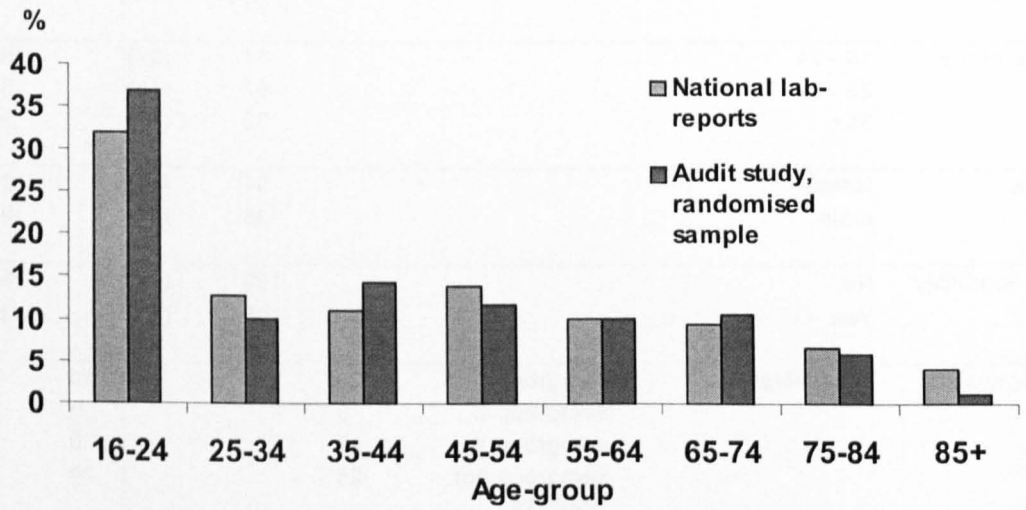
* 15 (14%) of patients with meningitis alone did not have a laboratory confirmed diagnosis ^ Total number in the 3rd column adds up to 191 due to rounding error induced by the weightin

For most of the cases (no.=102; 54%) the diagnosis was solely based on clinical picture, with no laboratory confirmation (no isolate, or other test: PCR, CSF/blood

smear). This percentage was lower in cases of meningitis alone (14%) than in cases diagnosed with septicaemia (solely or both). The most frequent causative organisms identified were *N. meningitidis* (32% of confirmed cases) followed by *S. pneumoniae* (13%)

The age distribution of the study cohort was similar to the national surveillance data (Figure 6.1), as was the gender distribution (51% of the cases were male).

Figure 6.1 - Age distributions of the hospital review sample and national surveillance data.



For 67 cases there was a record of patients' occupation. Of these, the most frequently recorded occupations were 'student' (n = 35, 52% of records); 'housewife' (n =10; 15%); 'retired' (n =5; 7%). 7 (10%) cases were classified as professionals and 10 (15%) as manual skilled & non- skilled workers.

6.4.2 Examination of the clinical parameters of the patient population

Neck stiffness was present in 69% (100/144) of cases in which it was recorded as having been examined, whereas a fundus examination was done in 104 cases and papilloedema was positive in 13 cases (in 9 cases it was not possible to examine). A neurological examination was done in 133 cases, and a focal sign was recorded to be present in 13% (10/133) of these cases. GCS was measured in 144 cases and

the mean value was 13 (s.e. 0.97; median 14); the lowest value recorded was 3. Intravenous antibiotics. were given throughout the treatment course in 157 cases and the fluid management plan was recorded in a majority of cases (110/190). Table 6.7 presents the frequency of diagnostic investigations performed in the study cohort.

Table 6.7 - Diagnostic investigations in the cases of CABM and MS, England and Wales, 2000 – 2001.

	Investigation	%	95% CI	N
Clinical sings	Pulse	92	88 to 96	190
	Temperature	85	79 to 97	190
	Systolic bl. pressure	93	90 to 97	190
	Rash	91	86 to 95	190
	Respiratory comprise	44	35 to 53	190
	Neck stiffness	76	67 to 86	190
	Papilloedoema	50	67 to 86	190
	Neurological examination	70	63 to 78	190
	GCS	73	66 to 80	190
	Capillary refill time	4	0 to 8	190
LP	Opening pressure	62	50 to 73	62
	WCC	100	99 to100	112
	WCC differential	98	94 to 100	85
	RBC	100	99 to 100	100
	G stain	98	95 to 100	84
	Protein	99	97 to 100	104
	Sugar	100	99 to 100	100
	CSF Culture	97	90 to 100	59
	CSF PCR	69	48 to 89	61
Blood	CRP	77	63 to 91	149
	Blood PCR	57	37 to 77	106
	Blood sugar	92	8 to 95	162
	FBC Hb	100	99 to 100	181

	FBC WCC	100	99 to 100	183
	Clotting	86	80 to 91	190
	Platelet	99	98 to 100	179

Mean pulse rate was 98.3/min (s.d. 1.3), temperature 37.8 Celsius (s.d. 0.74), mean systolic blood pressure measured 127.8 mmHg (s.d. 2.61); diastolic 71.6 mmHg (s.d. 1.09); a rash was recorded in 31 cases; peripheral perfusion was measured as a capillary refill time only in 2 cases, and in 81 cases by other methods.

6.4.3 Clinical practice

Multiple elements of the diagnostic and management process from first assessment, early management through to prevention of secondary cases did not meet the recommended clinical practice standards. There was incomplete recording of clinical information across a range of parameters (Details of record keeping are presented further below in this section).

6.4.3.1 Pre-hospital management

48% of the patients (95% CI 39% to 56%) for which this information was recorded had seen a GP before hospital admission (Table 6.8). A suspected diagnosis of CABM or MS was recorded in 40% (95% CI 25% to 55%) and parenteral benzyl penicillin was recorded as given in the community to 20% (95% CI 11% to 29%) of these cases. Where bacterial meningitis or meningococcal septicaemia were diagnosed, benzyl penicillin was recorded as given to 84% (95% CI 56% to 96%).

Table 6.8 - Management of cases at GP practices, before admission to hospital.

Pre-Hospital management	Yes (%)
Seen by GP	79/164 (48)
GP observed rash	16/79 (19)
GP suspected diagnosis	32/79 (40)
GP administered Benzyl Penicillin	17/85 (20)

6.4.3.2 Hospital management

First assessment in secondary care

115 (71%, 95% CI 65% to 77%) of cases were seen in emergency departments, the remainder were admitted directly to medical assessment units or other wards.

For most of the patients the first assessment was made by a Senior House Officer (SHO), followed by a Specialist Registrar (SpR), whilst a consultant made the first assessment in only 2 cases (see Table 6.9).

Table 6.9 - First assessment by medical staff.

		No. (%)
First assessment by	**JHO**	8 (4)
	SHO	93 (49)
	SpR	50 (26)
	Consultant	2 (1)
	Not known	37 (20)

The time to medical assessment, appropriate diagnosis and prompt administration of parenteral antibiotics varied considerably (Table 6.9). There was considerable variation in the speed and accuracy of the first assessment. For example, the median

time from arrival to first assessment was 45 min, but with i.q.r 10min to 1h 50min. Similarly, the interquartile range for the time from arrival to receiving intravenous antibiotics was 15m to 3h.

Table 6.10 – Clinical features and vital signs recorded

			Yes	No	Not recorded	Of all cases, % [95% CI] with recorded information
On first assessment	clinical features	neck stiffness	103	47	40	79 [70, 86]
		neurological examination	123	11	56	71 [62, 78]
		fundus examination	104	12	74	61 [57, 70]
		rash	91	82	17	91 [86, 95]
			Recorded		Not recorded	
	vital signs	conscious level (GCS)	143		47	75 [67, 82]
		pulse	174		16	92 [86, 95]
		temperature	159		31	84 [77, 88]
		blood pressure	177		13	93 [88, 96]
		respiratory rate	88		102	46 [34, 59]
		capillary refill time	5		185	3 [1, 7]
			Yes	No	Not recorded	
Microbiological investigations		blood culture	150	3	37	81 [74, 86]
		throat swab	56	71	63	67 [58, 75]
		lumbar puncture	120	65	5	97 [94, 99]

A differential diagnosis including CABM or MS was recorded in 82 (56%, 95% CI 45% to 67%) cases. Overall, parenteral antibiotics were administered to 56% (95% CI 46% to 66%) of cases within one hour of first assessment but when a diagnosis of CABM or MS had been made, were administered to 86% (95% CI 72% to 100%).

Severity of illness assessment

Of all cases of CABM and MS in this study (total 190) a full severity assessment was made in 18 (10%, 95% CI 5% to 15%) of them, whilst a partial assessment of severity (as defined in Chapter 3) was done in 63 cases (33%, 95% CI 25% to 39%).

Although 68 (81%, 95% CI 70% to 92%) severely ill cases underwent some form of severity assessment, only 27%, (43/162) underwent a full severity assessment. Amongst meningitis cases 34% (95% CI 22% to 46%) were assessed fully or partially for severity, whilst amongst the meningococcal septicaemia cases this was done in 75% (95% CI 61%, 89%) of cases. Overall, the time to assessment by an ICU team was highly variable (i.q.r between 35m to 8h 30m) but varied less for severely ill cases (35m to 2h 35m).

Lumbar puncture and CT Brain Scan

A lumbar puncture was performed in 65% (120/185; 95%CI 54 to 75) patients overall and in 79% (117/149; CI 70% to 85%) patients with bacterial meningitis, with or without septicaemia, whereas in patients with meningitis alone 11 (10%) of them did not undergo a LP.

Among the 35 cases where all the relevant information was available, 14 underwent lumbar puncture in the presence of either papilloedema, a GCS of ≤ 10, and/or focal neurology. Of the 126 cases for whom the information was available, 81 (64%, 95%CI 55% to 82%) underwent CT brain scan before LP. The exact time when the CT was performed was not generally recorded and therefore it was not possible to assess whether CT contributed to the delay in administration of antibiotics.

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6.4.3.3 Recording of clinical findings and investigations.

There was incomplete recoding of clinical information across a range of parameters (Table 6.11). Record keeping was classified as good in 125 (68%) medical notes.

Table 6.11 - Record keeping of clinical management in the case-notes of patients.

Record keeping (N. 185)	%	95% CI
Bad	2	0 to 5
Fair	30	23 to 37
Good	67	60 to 75

The quality of record keeping varied slightly and not significantly when the senior staff assessed patients. Table 6.12 presents the recording of the essential information (See Appendix 3) on clinical management of a case by the senior staff.

Table 6.12 - Essential information recorded if assessed by senior staff.

	Essenital info recorded % (95% CI)
Assessed by a consultant	65 (50.1 to 82.8)
Assessed by a	76 (59.9 to 95.1)

6.4.3.4 Treatment with antibiotics

In the 179 cases where the antibiotic administered was recorded, cefotaxime or ceftriaxone were the most common first-choice parenteral antibiotics (n=117, 65%), followed by a combination of Benzyl Penicillin and cefotaxime (n=44, 25%). None of the 4 cases with a recent history of travel to high-prevalence antibiotic-resistant countries, including Spain and USA, was prescribed vancomycin.

6.4.3.5 Consultant's speciality

The specialty of the consultant in charge was available for 153 cases, the majority were general physicians (82, 54%). Consultant geriatricians and neurologists were in charge of 16 (10%) cases each; followed by cardiologists in charge of 11 (7%). In 37 cases it was not possible to retrieve this information.

6.4.3.6 Notification and antibiotic prophylaxis

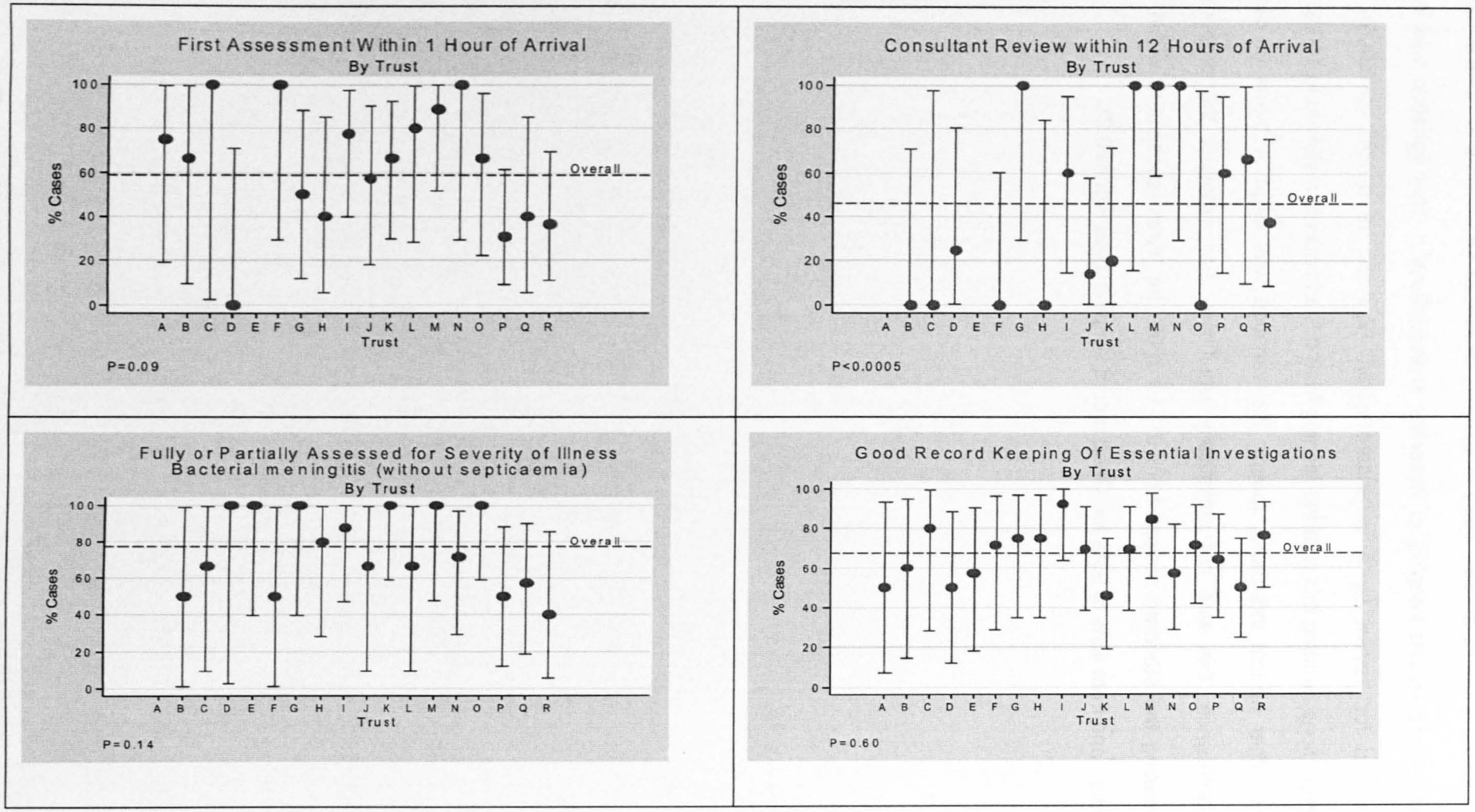
In total 111 cases where reported to a consultant for communicable disease control (CCDC - a medical consultant responsible for the surveillance, prevention and control of communicable disease) at some stage. However, this notification was done within 24 hours of diagnosis (as per recommendation) in 64 cases of 72 where information on the time of reporting was available (86%, 95% CI 76% to 93%). 58 cases received rifampicin and an additional 23 cases received ceftriaxone as part of treatment alone, so that in total 81 (43%, 95% CI 35% to 50%) of all 190 cases reviewed, and 76% (95% CI 62% to 87%) of the 106 meningococcal meningitis or meningococcal septicaemia cases received recommended antibiotics to eradicate carriage before discharge.

6.4.4 Variation in clinical practice between hospitals

Numerous differences in the clinical management of CABM and MNS between NHS trusts were observed. Figure 6.2 highlights the variation between the 18 hospitals in four indicators, namely: 'First assessment within 1 hour of arrival', 'Consultant review

within 12 hours of arrival', 'Fully or partially assessed for severity for CABM cases' and 'Good record keeping of essential investigations'. This variation was most marked for 'review by a consultant within 12 hours of arrival' ($p<0.005$), the proportions meeting this criterion ranging from 0 % of patients reviewed to 100%. For the other clinical indicators, though the variation was large in terms of clinical significance, this was not statistically significant. For example, the proportions meeting the standard ranged from 0% to 100% for 'First assessment within one hour', and from 45% to 95% for 'Good record keeping' (see Figure 6.2).

Figure 6.2 – Variations in clinical practice between the trusts



6.4.5 Outcomes

6.4.5.1 Length of stay

The median length of stay in hospital was 10 days (i.q.r. 7 to 16 days).

6.4.5.2 Case-fatality

In total there were 21 deaths in the cohort, constituting an overall fatality rate of 11% (95% CI 7% to 17%).

Diagnosis

For meningitis only cases, the fatality rate was 14%, (X out of Y, 95% CI 9% to 19%); whilst for MS it was 13%, (X out of Y, 95% CI 6% to 21%). Among the 79 cases managed at HDU/ICU there were 14 deaths (CFR 18%; 95% CI 11% to 28%).

Causative organism

The highest fatality rate by causative organisms was recorded for the cases with no isolate 25%, (95% CI 15% to 37%). However, where a organism was isolated *S. pneumoniae* was the commonest cause of death with a case fatality rate of 18% (95% CI 11% to 28%).

Age

Case fatality rates were highest among individuals 75 or more years old (38%, 95% CI 7% to 71%) compared with 6% for those aged 55 - 64 years old (see Table 6.12)

Table 6.13 - Case fatality rate by age group

Age group	Fatality %	95% CI	N
16-24	9	3 to 15	71
25 - 34	13	0 to 31	19
35-44	6	0 to 17	27
45 - 54	12	0 to 28	22
55 - 64	6	0 to 18	19
65 - 74	10	0 to 22	19
75 - 64	39	7 to 71	11
85+	0	~ to ~	2
16 +	11	7 to 17	190

6.4.5.3 Long term sequelae

Of the 190 patients, 65 (34%) had long-term sequelae at discharge (many had multiple sequealae), including: hearing impairment (n=30), other neurological impairment (34), severe scarring or plastic surgery (8), loss of digits or limbs (6) and other sequelae such as renal failure, behavioural change, chronic arthritis or peripheral ischaemia (16).

6.5 Discussion

6.5.1 Strengths and limitations of the study

This study was based on a randomly selected sample of national acute NHS trusts. I examined contemporaneous data, reviewing medical records of patients, including A&E, and nursing notes. The general characteristics and age distribution of this cohort was similar to that expected from national surveillance data (Chapter 4).

CABM and MS are relatively uncommon in adults, therefore a prospective study would have not been feasible. My findings were limited by the quality of case note keeping. This was the main limitation which impaired the analysis. Some were particularly affected, such as: a) severity assessment was restricted to those parameters that were commonly documented; b) the assessment of timeliness of the management indicators.

The study was retrospective, hence did not affect the quality of records kept in the medical notes. A prospective study would have most likely ensured that the essential medical indicators were more completely recorded. However, the study would then not have been representative of real management practices.

The poor medical record keeping is also likely to both affect and reflect inadequacy in medical practice, and it is likely to increase the risk of error (Mann, 2003; Huston, 2004).

6.5.2 Conclusion

This study revealed many areas of clinical practice where standards of care do not meet the recommended standards. The study also emphasized a need for improvement in several areas of clinical practice relating to CABM and MS, these will be discussed in more detail Chapter 8, Discussion and in Chapter 9 Recommendations.

Chapter Seven

Association of clinical management with the outcome of community acquired bacterial meningitis and meningococcal septicaemia in adults in England and Wales

Table of content

7.1 Introduction

In the previous chapter I showed that many of the key clinical management recommended standards are not met in current clinical practice.

There is a current debate around the evidence on the benefit of early recognition of CABM and MS and, in particular, early antibiotic treatment (Harnden et al. 06). It is, though, recognised that much of this lack of evidence is due to inherent limitations of observational studies, including confounding and lack of prospective studies. These problems are compounded by the inappropriateness of randomised studies.

Much effort in policy making and improvement of health-care services is put into agreeing standards of care (Shekelle and Schriger 1996). However for many of the recommendations the evidence on whether they do improve the outcome of the disease is not robust, or is unavailable. Unless randomised controlled trials are undertaken it is difficult to assess the effect of standards of care on outcomes.

Observational studies assessing the effect of a treatment or exposure are often subject to bias and confounding which can be difficult to eliminate or control for using standard statistical methods, including multivariate models. These conventional statistical techniques may not adjust for the important prognostic characteristics between the treatment subjects, and the remaining bias may limit valid causal inference. Use of propensity scores models is considered to better adjust covariates between the groups and reduce bias, especially when there are many relevant covariates and data on outcomes are sparse. Retrospective studies, such as the review I undertook on the clinical management of CABM and MS also are subject to missing data. I attempted several approaches to dealing with missing data in this chapter.

The purpose of this chapter is to examine the association of clinical management indicators with the outcome of the disease and compare the statistical approaches in this context.

7.2 Data and Methods

7.2.1 Data

The data used in this part of the research are from the review of case-notes from randomly selected hospitals across England and Wales. These are described in details in Chapter 3 and are the same as the data used in Chapter 6. For the purpose of this investigation I had to generate a few new variables, such as:

a) Clinical predictors:

High glucose; high systolic pressure; high blood urea; - these variables were generated as a dichotomous variable based on the original continuous variable, using the recommended normal range of clinical parameters.

b) Management indicators:

Continuous: time to first assessment; time to antibiotics; time to first diagnosis; time to consultant / ICU review – these were derived from time of arrival to the time of the performed indicator (for details see Chapter 3);

Dichotomous: first assessment within one hour; antibiotics within one hour; diagnosis within one hour; consultant / ICU review within 12 hours are based on the defined standards are generated from the original data as above.

7.2.2 Methods

For details of the data collection, see Chapter 3.

I excluded cases where death occurred in less than 6 hours as it was considered that the impact of clinical management could not be examined in these cases.

7.2.2.1 Outcome

Outcome was defined as adverse if the patient died or survived with the defined (see previous chapter) long-term sequelae (McMillan, Lin et al. 2001). Outcome was good if the patient recovered and without the defined long-term sequelae. The Outcome

variable was coded 1 if outcome was adverse, 0 if outcome was good. Thus the odds ratios presented are for adverse outcomes.

7.2.2.2 Severity of illness

Illness was defined to be severe if cases met the following criteria. For the meningitis only cases: GCS of 10; low pulse rate (<60) and high systolic pressure (>140); low platelet count >100/m^3.

For the septicaemia cases: GCS of 10; low systolic pressure (<90mmHg) and no neck-stiffness; low WCC (<10mm^3) and low platelet count (<100/mm^3).

7.2.2.3 Clinical management indicators examined

I identified four main clinical management indicators to be examined against the outcome. These were: early medical assessment; early suspected diagnosis; early antibiotic treatment; and review by a senior clinician including consultant and ICU team.

7.2.3 Statistical methods

These are described in full detail in Chapter 3.

Odds ratios and 95% confidence intervals were derived from logistic regression models, adjusting for random hospital effect. Univariable analysis included only the exposure of interest, i.e. one of the clinical management indicators examined with the outcome. Multivariable analysis was used to adjust this association for possible confounders. The latter were identified from the analysis of clinical parameters associated with the outcome; all the relevant clinical parameters for which I collected data were examined using logistic regression analysis.

7.2.3.1 Dealing with the missing data

I used two different approaches to dealing with missing data, as follows:

Assuming best and worst scenario for subjects with no data on a clinical management indicator (Bridewell, Langley et al.; Collaboration 2002; Gamble and Hollis 2005).

7.3 Results

A total of 187 cases where included in the analysis for this chapter (3 cases were excluded as they died within 6 hours of admission).

7.3.1 Prognostic factors associated with outcome

Several clinical features were found to be associated with the outcome, namely: age, high systolic blood pressure, GCS, high blood urea, high blood glucose, causative organism. These are referred to as 'the prognostic factors' (Table 7.1).

Table 7.1- Prognostic factors associated with outcome, statistically significant in univariate analysis.

Prognostic factors associated with outcome, statistically significant in univariate analysis			
		N (n)	OR (95%CI)
Age	continuous	187 (44)	1.04 (1.02 to 1.05)
	<65yrs	155 (61)	1
	>65yrs	32 (22)	3.39 (1.50 to 7.65)
Causative organism	*Neisseria meningitidis*	63 (19)	1
	Streptococcus pneumoniae	25 (18)	5.41 (1.93 to 15.16)
	Other isolated organisms	4 (2)	2.10 (0.27 to 16.10)
	Clinical diagnosis only	95 (44)	1.00 (0.56 to 1.79)
GCS	continuous	140 (49)	0.89 (0.79 to 0.99)
	>=13	73 (30)	1
	<13	67 (39)	1.99 (1.02 to 3.91)
Blood Pressure / Systolic	continuous	187 (83)	1.01 (1.00 to 1.02)
	<=90mmHg	118 (44)	1

	>90mmHg	56 (36)	0.94 (0.82 to 1.08)
Blood Urea	continuous	140 (52)	1.13 (1.04 to 1.23)
	Low	107 (36)	1
	High	80 (47)	2.81 (1.54 to 5.11)
Blood sugar	continuous	14 (66)	1.16 (1.03 to 1.31)
	Low	118 (48)	1
	High	69 (35)	1.5 (0.82 to 2.73)
Neuromuscular convulsions	Y/N	75 (8)	9.11 (1.04 to 79.96)
N - number in analysis			
n - number with adverse outcome			

The reference level is No (entered as 0, lower entry, in the data).

7.3.2 Clinical management factors associated with outcome

The only clinical indicator that was associated with outcome was diagnosis within 1 hour, as first assessment was defined. Of the 111 cases that had a diagnosis made in the first hour, 48 had an adverse outcome; the odds ratio of 0.45 (95% CI 0.22 to 0.93 Table 7.2) indicated an increased benefit from early diagnosis. However in the multivariate analysis controlling for the clinical predictors listed above, this association weakened and was not statistically significant (Table 7.2).

No other clinical indicator examined appeared to be associated with the outcome of the disease, in either univariable or multivariable analysis. (see Table 7.2).

While the odds ratios for the association between adverse outcome and clinical management indicators were generally not significant, most tended to indicate a protective effect (Table 7.2).

Table 7.2 - Uni and multi variable analysis of association between clinical management and outcome in bacterial meningitis amongst adults.

Uni and multi variable analysis of association between clinical management and outcome in bacterial meningitis amongst adults.				
Clinical management indicator	Yes (a)	N (n)*	OR (95% CI)	OR (95%CI) adjusted"
First assessment within 1 hr (Y/N)	58 (24)	187 (118)	1.01 (0.94 to 1.07)	0.96 (0.87 - 1.07)
Diagnosis on first assessment (Y/N)	111 (48)	154 (101)	0.45 (0.22 to 0.93)	0.52 (0.17 - 1.56)
Antibiotics on first assessment (Y/N)	67 (26)	103 (73)	0.99 (0.43 to 2.29)	1.55 (0.41 - 5.85)
Consultant review within 12 hours (Y/N)	28 (12)	118 (187)	1.001 (0.937 to 1.085)	0.979 (0.881 - 1.088)
ICU review within 12 hours (Y/N)	33 ()	()	0.988 (0.906 to 1.078)	1.016 (0.903 - 1.145)
Specialist^ review within 12 hours	47 ()	()	0.969 (0.893 to 1.051)	0.942 (0.842 - 1.053)
Yes - number with the indicator performed			NA: Not appropriate	
a - number with adverse outcome				
N - number in unadjusted analysis			^ Consultant or ICU team	
n - number in adjusted analysis			" age, GCS, BP, Urea	

7.3.3 Dealing with the missing data

7.3.3.1 Assuming the best vs. worst scenario

Assuming that subjects for which there was no relevant data did have the recommended clinical management indicator present (best scenario) generally resulted in more protective associations, though for none of the indicators examined did this result in a significant association (Table 7.3).

The pattern was less consistent when it was assumed that subjects with missing data did not have the recommended clinical management indicator present (worst scenario); these associations were not significant either (Table 7.3).

Table 7.3 - Multivariable analysis of association between clinical management and outcome in bacterial meningitis amongst adults - assuming the best or worst scenario for the missing data. (N=187)

Multivariable analysis of association between clinical management and outcome in bacterial meningitis amongst adults - assuming the best or worst scenario for the missing data. (N=187)		
Clinical management indicator	OR (95% CI) best	OR (95% CI) worst
Assessment within one hour from arrival	0.77 (0.30 - 1.98)	0.96 (0.87 - 1.07)
Diagnosis within one hour from arrival	0.41 (0.14 - 1.21)	1.19 (0.48 - 2.92)
Antibiotics within one hour from arrival	2.57 (0.77 - 8.54)	0.51 (0.22 - 1.18)
Consultant review within 12 hrs from arrival	0.98 (0.88 - 1.09)	0.98 (0.88 - 1.09)
ICU review within 12 hours	1.03 (0.91 - 1.16)	1.03 (0.91 - 1.16)
Specialist^ review within 12 hours [$]	NA	1.58 (0.65 - 3.83)
[$] - predicts failure perfectly!		

7.4 Discussion

Would the outcome of cases of CABM and MS actually improve if the recommended standards of care are met? In an initial analysis of the four key indicators as part of the review of the clinical management (presented in the previous Chapter) I found no significant association with the outcome. This led me to explore this question further.

7.4.1 Strengths

This part of my research dealt with a very important question – that of the effect of clinical factors and clinical management in the outcome of the disease (CABM and MS).

The identification of clinical predictors is consistent with other studies in adults with CAB M and MS. I found that age, causative organism (and *S pneumoniae* in particular), blood pressure, conscious level and blood level of glucose and urea were associated significantly with a adverse outcome (van de Beek, de Gans et al. 2004).

Much effort is directed to developing clinical guidelines and in implementing them in clinical practice (Shekelle and Schriger 1996; Shekelle, Woolf et al. 1999), hence it is important to have evidence that those efforts are appropriate, i.e. have the desired impact (Raine, Sanderson et al. 2005). The evidence for this is lacking, particularly so in the management of CABM and MS, where there is a recent debate about some of the recommended practice, i.e. early management with a.b (Hahne, Charlett et al. 2006; Harnden, Ninis et al. 2006). For this reason, I sought to address this issue in this part of my thesis.

7.4.2 Limitations

The major limitation of this part of the study was its low power, further reduced by missing data. Incomplete data is a common problem with regard to clinical management (Davenport, Dennis et al. 1995), as was shown in the previous chapter. However the extent of the missing data on variables of specific interest, such as the times to intervention in clinical management, was very high. This compromised even the methods used to dealing with the missing data.

I attempted to assess the impact of missing data by carrying out a sensitivity analysis, assuming best and worst scenarios for the missing clinical management indicator. This showed the estimated odds ratios for the effect of the clinical management to lie in the direction that would be expected, though the 95% CI were wide and inclusive of the value of no effect, i.e. 1 (Collaboration 2002). The impact of missing data was also felt on the clinical indicators; a similar best/worst scenario could have been used for these (Personal communication, Prof D Lawlor, 2008) (Table 7.3).

Another approach to dealing with missing data is (multiple) imputation. This method of dealing with missing data is widely recommended, and is based on the assumption that the subject with missing data are similar to their cohort of cases with respect to the variable in question (Schafer 1999; O'Rourke 2003). As noted above the extent of the missing in my study data was, particularly for some indicators, very high. There is no one acceptable amount of missing data, below which imputation will not be effective. It is generally considered that when the rate of the missing data is over 50% there is not much benefit in applying multiple imputation for dealing with missing data (Personal communication Prof J Sterne, Prof D Lawlor, 2008). An approach ot the impiutation of the missing data would have been to estimate the average value of the time to intervention for the subjects with missing data and impute this average where data were missing (Schafer 1999, Schafer and Graham 2002).

I consider application of the propensity scores analysis, which is considered as another appropriate approach to examinig risk associations in observational studies as it provides a simpler and robust way to control for multiple clinical variables that influence both treatment and outcome – i.e. confounders. Propensity scores can be described as the conditional probability that a subject will be treated, based on an observed group of underlying subjects' characteristics (prognostic factors) (Kurth, Walker et al. 2006).

However, as the logistic regression analysis, and attempts to deal with the missing data were not indicative of any promising or sensible results in more complex analyses, I did not carry out the analysis of the propensity scores. The approach would have been to obtain the propensity score from the logistic regression model including the following pretreatment variables: age, causative agent, clinical- severity: low platelet count. Then match the subjects using a criterion e.g. +-0.05 (depending on results of propensity score form log regression model) of the propensity score and grouped as such (Heckman et al. 1997) for further analysis.

Neither of these methods, i.e. imputation of the missing data or propensity scores analysis, would help overcome the essential problem with these analyses, which is that they are under-powered. This is essentially as the primary aim was not to investigate the impact of management on outcome, but to describe management (see Chapter 3, Calculation of study sample). Nonetheless my study suggests that management might influence outcome, but a larger study is needed to estanlish this conclusively.

Chapter 8

Discussion

Table of content

8.1 Introduction

> "Seeking to know is only too often learning to doubt."
>
> Antoinette Deshoulieres

In this chapter I will contextualise the findings from my research, compare them with other adequate published reports and discuss the implications for practice and policy. I will start with the main findings from the examination of the epidemiology of CABM and MS, to follow with the results and their application from the capture-recapture analysis. Once the epidemiology of the disease is addressed I will move to its clinical management. I will address the main findings from the review of clinical management, comparing them with other similar research and addressing their relevance in improving clinical standards. I will then discuss the possible association of clinical management with the outcome of the disease. I will then debate how this research fits with an improved understanding and hence improved outcome from CABM and MS.

In the next part of this chapter I will review the strengths and weaknesses of this research. Lastly I will address how this research can be taken further.

In the next chapter I will discuss the specific recommendations for policy, practice and further research.

8.2 Overview of this research

This study provides the first nationally representative examination of the epidemiology and clinical practice in relation to CABM and MS in adults in England and Wales. Previous work has been largely focused on meningitis in children and mostly reviewing their management in the community, i.e. general practice or describing the clinical picture in adults (Thompson, Ninis et al. 2006) (Noah 1987; Rosenstein, Perkins et al. 1999). An examination of the epidemiology of CABM in adults was done for Scotland, showing many similar aspects of changing epidemiology to what my study showed,

however this did not include an assessment of clinical practice (Kyaw, Christie et al. 2002). Generally the published literature about the disease in adults was scarce.

Even though rare, the burden of CABM and MS in adults is relatively high: with an overall fatality from the disease of over 10%, but reaching nearly 40% in the older people (Cartwright, Reilly et al. 1992; Heyderman, Lambert et al. 2003). This was demonstrated with the analysis of the epidemiologic data, as well as through the hospital case-notes review. Another major burden of the disease is the long-term sequelae, and I was able to measure this through the hospital case-note review, as well as compare it with other published reports, showing that over the third of the cases that survived had evidence of a form of long-term sequelae (Grimwood, Anderson et al. 1995; Erickson, De Wals et al. 2001; van de Beek, Schmand et al. 2002).

My research encompassed most of the aspects of the disease that are important when considering an overall approach to reducing the burden of a disease – epidemiology, accuracy of the available data, clinical management practice and preventative strategies.

The main findings of this research are:

- A changing epidemiology over the years, with regard to both the causative organism and the population groups affected.
- Routinely reported incidence and mortality is underestimated.
- The recommended standards were not widely achieved in a number of key areas throughout the diagnostic and management process, compared to the guidelines.
- The inconsistency and the lack of the record keeping in the hospital medical practice.
- I did not find a significant association of clinical practice indicators with the outcome of CABM and MS. This, largely due to limitations with the medical record keeping, but also the lack of statistical power of the study to measure this association.

8.3 Is the epidemiology of CABM and MS changing and what are its implications?

8.3.1 Overview

Accurate ascertainment of a changing epidemiology requires surveillance of a large population over a long time-period. The 12 year analysis of national routine surveillance data, presented in Chapter 4, shows that overall the incidence rate of CABM and MS among adults has not changed much (95% CI for RR 0.99 to 1.03) annually in England and Wales between 1991 and 2002; there were, however, opposite trends for CABM (decreasing 4% annually, 95% CI for RR 0.94 to 0.98) and MS (increasing 7% annually, 95% CI for RR 1.03 to 1.11). This increase in MS incidence is largely explained by an upsurge in meningococcal disease during the well-documented national epidemic in the late 1990s. The possible explanations for this are addressed further below.

CABM is occurring in an increasingly older population and is associated with a case fatality, which remains unacceptably high overall, exceeding 23% in those over 55 years (Durand, Calderwood et al. 1993).

During the second half of the last decade, meningococcal disease reached high incidence rates (epidemic levels according to some authors) in the UK alongside similar trends in several European countries (Connolly and Noah 1999; McVernon, Howard et al. 2004) The UK MenC vaccine programme was then introduced and has been highly effective (Ramsay, Andrews et al. 2003). In the year following completion of the introductory programme, confirmed cases of invasive group C disease fell by 85% overall and deaths in those aged less than 20 years fell by 90%. In contrast, the burden of serogroup B disease remains constant, with an apparent increasing in number of cases during late 1990s early 2000 (however, the number of cases in adults has been falling since, though this is outside the study period for this research) (HPA 2009). The data presented here demonstrates the impact of this epidemic on the adult population,

which although concentrated on 16-24 year olds remains prominent across all age groups. In line with previous studies, there has been a consistent shift of MD towards older ages (Harrison, Pass et al. 2001), with older women being at increased risk compared to men (Rosenstein, Perkins et al. 1999).

8.3.2 The varying trends in incidence by causative organisms

It is noteworthy that there are apparently contrasting trends in the laboratory reporting of meningococcal septicaemia and meningitis. These could be explained by a reduction in the number of diagnostic lumbar punctures performed (Ramsay, Kaczmarski et al. 1997; Jolly and Stewart 2001) leading to the under reporting of meningitis or by a real change in the clinical presentation of meningococcal disease with more septicaemia and fewer meningitis cases. The observation that the ONS notification rates, a clinician based reporting system, did not follow a significant decreasing trend for meningococcal meningitis (as seen for the laboratory reports) suggests that the trend in laboratory reports represents a change in diagnostic practice rather that a change in the biology of the disease (Ramsay, Kaczmarski et al. 1997).

With regard to the incidence by the causative organisms of CABM, during the same time period there has been a decrease in meningitis caused by *H. influenzae* and *L. monocytogenes,* whilst tuberculous meningitis has had a small but significant increase in the incidence.

The decline in invasive *H. influenzae* infection after the introduction of routine Hib vaccination has been dramatic amongst paediatric populations (Teare, Fairley et al. 1994; Heath and McVernon 2002). My data reveal a reduction in the incidence of *H. influenzae* CABM amongst an adult population who would not have received Hib vaccine. This supports the suggestion of a herd immunity effect observed in both US and UK populations (Barbour 1996; Wenger 1998; Sarangi, Cartwright et al. 2000), presumably resulting from a reduction in nasopharyngeal colonisation (Mohle-Boetani,

Ajello et al. 1993). During the early 2000s there was a small but constant rise in Hib cases; raising the possibility that the effect of the vaccine on the unimmunised population may also break down, again underlining the importance of continued surveillance (Ramsay, McVernon et al. 2003). Following this increase in number of cases a Hib booster campaign was undertaken in 2003, which helped to re-establish herd immunity in the UK, and provided evidence for the routine boosting for Hib at 12 months of age (Ladhani, Slack et al. 2008; McVernon, Ramsay et al. 2008).

Over the last two decades there has been a global resurgence of tuberculosis. The 9% annual increase in tuberculous meningitis revealed in this study is the tip of a TB iceberg (Handysides 1997), in which there has been a reversal of previously falling incidence of the disease in the UK. This is a worrying trend: TB meningitis is more likely to be associated with HIV co-infection and, in those that survive, is associated with a very high morbidity (Rose, Sinka et al. 2002). Although multi-drug resistance TB remains uncommon in the UK (Djuretic, Herbert et al. 2002), should this emerge amongst this enlarging population of meningitis cases, the results would be devastating.

The risk of meningitis caused by *L. monocytogenes* amongst pregnant women, the elderly and the immunocompromised has led to the recommendation that antibiotics such as high dose ampicillin are added to empirical therapy for CABM (Begg, Cartwright et al. 1999). The data I have presented here, mirror the reductions in invasive disease seen in Scotland and the US (Kyaw, Christie et al. 2002; 2003). I have presented a comparison between my study and the Scottish study (kyaw et al 2002) in Chapter 4, section 4.5.2.a Although current recommendations do not warrant modification at this stage it is reassuring that better regulation of contaminated foods and dietary recommendations for high-risk individuals issued by the UK Department of Health and the US Centres for Disease Control have been effective.

S. pneumoniae is the most prominent aetiological organism and is associated with a fatality of over 30%. The true burden may be significantly underestimated. Using

capture-recapture analysis, which was presented in Chapter 5, I demonstrated an almost 2 fold under-ascertainment of both incidence and mortality from adult pneumococcal meningitis in England by the national laboratory and clinically-based reporting systems. In addition, the sensitivity of these systems to capture cases occurring in the over 85 year olds had a tendency to be lower than in the younger population, though the numbers in analysis for this age group were small and no statistical significance was reached. These findings emphasise both the need for diagnostic vigilance and evaluation of vaccination programmes in this age group.

There is a significant burden of co-morbidity in an increasingly elderly population in many industrialised countries, including the UK. The data presented in Chapter 4 suggests a shift in the burden of bacterial meningitis to this population, with proportionately more cases occurring amongst older ages in the recent years. The case-fatality rate, though, did not exhibit the same upwards trend with increased age, i.e. case-fatality rates decreased over time for the older ages, but not so for the younger ages. One of the obvious explanations is that of the aging population effect, i.e. there are proportionately more older people in the recent years of the 12 year study period. However the data is presented in rates per 100,000 people, which should account for the proportionate distribution of age-groups over the time, and the incidence is low to suffer from such an effect. Another explanation is that particularly meningococcal disease, which actually accounts for most of the cases, occurs in epidemic cycles and the epidemic of the mid nineties, which at time mostly affected children and young people, might have been tailing off amongst the older age groups. The recent conjugate vaccination programmes have resulted in long-term immunity and have had an effect in carriage and herd immunity, which could have had provided some protection of the younger age groups (e.g. 16 to 34 year olds) in the few years following the epidemic of the early 90s. A possible explanation accounting for the falling overall case-fatality over the years is that the meningococcal epidemic in the first half of the study period, was

primarily caused by *N.meningitidis* group C, which is associated with higher fatality. It is possible, though I did not analyse the data by serogroups, that proportionately more cases in the later part of the study period where caused by other serogroups, particularly serogroup B, with lower fatality then serogroup C, this was shown in an early review of MD following the introduction of Men C campaign in under 18s in 1999 (Ramsay, Andrews et al. 2001). The apparent decrease in case-fatality rate for older ages but not so for younger ages (16-24) has been reported by other studies (Harrison, Dwyer et al. 1999), a possible explanation is that Meningitis C, which has a higher fatality, is more common in younger people (Gold 1999; Ramsay, Andrews et al. 2001).

An additional factor that should be recognized in the epidemiology of infectious diseases in general, and hence in CABM and MS, is the effect of epidemics on disease estimates, namely incidence. Some, but not all of the causative organisms of CABM have a recognized potential for epidemics – these are mostly *N. meningitidis, Hib* and to a lesser extent *S. pneumoniae, M.Tuberculosis* and, though *L. monocytogeness* and *E. coli* can cause generally food-born outbreaks, the proportionate meningitis cases in these invasive diseases are almost not relevant for the epidemic transmission to have effect on the epidemiology of meningitis. Nonetheless, epidemiologic studies that have looked into the effect of epidemics in disease estimates have found only a marginal effect, and that standard methods that do not adjust for regular epidemics are valid (Whitaker and Farrington 2004).

8.3.5 The trends of lumbar puncture (LP) in examination of the epidemiology of CABM and MS

The exercise of validating the trends of LPs, that I undertook surveying the HPA laboratories in the SW, showed that the number of CSF specimens received by the laboratories (i.e. CSFs taken through LPs by the clinicians in patients with suspected diagnosis of meningitis) did not fall during the study period. This finding is also supported by the capture-recapture analysis, which did not show a trend of decreasing sensitivities

of the surveillance sources over time (Table 5.4). This exercise did not support possible suggestions that any fall in the incidence of CABM is due to the fall in LPs performed.

8.2.6 Implications of the changing epidemiology for policy and practice

This part of my research provided evidence for the changing epidemiology of CABM and MS among adults in England and Wales (though most aspects of the epidemiology are not significantly different in other parts of the UK) (Kyaw, Christie et al. 2002) . Vaccine programmes in children and young adults are likely to have a significant impact in the epidemiology of disease amongst adults, and other factors such as improved food hygiene, the re-emergence of TB and an aging population also all appear to be having an effect. This data emphasises the need for continuing enhanced surveillance and the need for constant re-evaluation of the age groups for which vaccination should be targeted. Vaccine programmes that take into account the continuing burden of disease throughout adulthood are required.

8.4 The under-ascertainment of CABM – what is its extent and how does it affect the sensitivities of surveillance sources?

8.4.1 Results of the capture – recapture analysis in context

The capture-recapture analysis provided evidence of under ascertainment of both incidence and mortality from adult pneumococcal meningitis amongst adults in England by the national laboratory and clinically-based reporting systems. All data sources compared in the study captured around half of the estimated cases and/or deaths in the population. It seems that, from the trend analysis for HES and ONS reported deaths, increasingly more deaths have been occurring at hospitals across the years. This might suggest that more cases are reaching hospitals, even though probably not early enough. My findings are similar to capture-recapture estimates of bacterial meningitis in Italy (Faustini, Fano et al. 2000), and the estimates of case-fatality rates (24%) are similar to those published elsewhere (16-31%) (Berg, Trollfors et al. 1996; Moberley, Holden et al. 2008) and comparative with a European wide study on meningococcal meningitis (Trotter, Samuelsson et al. 2005). An additional feature to give support to my findings is that I focused on the disease in adults, which is a lot less recognized then the paediatric CABM and MS, and therefore the rate of clinical ascertainment and hence reporting is likely to be lower. Hence, this capture-recapture analysis should be generalisable to other industrialised countries, with a similar epidemiology of adult pneumococcal meningitis and other forms of CABM, and similar surveillance systems.

Apart from incomplete reporting in the surveillance systems, under-ascertainment may arise from the absence of a specific diagnosis in the severely ill, particularly the elderly (Le Moal, Roblot et al. 2000; Davison, Crowcroft et al. 2002); the absence of a confirmed microbiological diagnosis (Newcombe, Cartwright et al. 1996); or misclassification of known pneumococcal meningitis as meningitis cause 'unspecified' or cause 'unknown'. An active surveillance study conducted in the United States concluded that deaths due

to invasive pneumococcal disease may be underestimated by 15-45% and suggested that these missed cases could potentially be reported as 'unspecified' deaths (Moore MR 2001).

This analysis did not show any trend of under-ascertainment associated with age. There seemed to be some decreasing sensitivity of surveillance sources from 16-24 to 75-84 age groups, though the confidence intervals overlap widely, suggesting no effect of age in the sensitivities of the data sources, though other studies have suggested an lower index of suspicion of diagnosis of meningitis in older ages (Davison, Crowcroft et al. 2002). I choose not to compute the CIs for the 85+ age-group owing to the scarcity of the data. However, it is likely that these would be been wide and overlapping with the younger age-group. Clinically it is thought that diagnosis of meningitis in the elderly is more difficult, not solely because of the complicated comorbidities that these patients present with. Other studies using capture-recapture method have found an underreporting associated with age, and severity (Hickman, Sutcliffe et al. 1999; Jarvis, Lowe et al. 2000). Similarly, a recent review of the published literature on the usefulness of the routine data sources in epidemiology of infectious diseases found that the reporting of infectious disease was most strongly associated with the type of the disease being reported and that the feasibility of a early distinguished diagnosis (Doyle, Glynn et al. 2002).

In support of the validity of my estimates of incidence and mortality is the estimated case-fatality rate from the capture-recapture method. The analysis yielded an estimate of the case-fatality rate of over 20%, which is in line with reported fatalities from other studies (Aronin, Peduzzi et al. 1998) and it is similar with case-fatality calculated from the routine surveillance data, presented in Chapter 4.

It is possible that some cases of pneumococcal meningitis might have been missed in the capture-recapture analysis as they might have had been confirmed through blood test rather then CSF (hence missed from the laboratory surveillance). However the aim

of my study was to examine the ascertainment of CABM in adults, which ultimately has an effect on the management of the disease. Hence, if clinicians have confirmed a pneumococcal infection with the blood test rather then CSF it is likely that this is reflected in the clinical management of the case (which might not be appropriate for meningitis).

8.4.2. Validation of matching in the South West region

This validation exercise, confirming the matching process of individuals' subjects between the data sources, validated my capture-recapture analysis. The individual laboratories were in position to cross check the records they had using further personal identifiers (then what I had) against the hospital records. They identified 2 additional matches, 2 incorrect diagnoses and 5 additional cases, and the capture-recapture estimate for the South West Region was unchanged as per my available data.

8.4.3 Possible implications on vaccine prevention

Pneumococcal meningitis, although rare in comparison to other forms of pneumococcal disease in adults, is associated with a high mortality and represents a reasonably robust indicator of the burden of invasive pneumococcal infection in the population (Aszkenasy, George et al. 1995). Therefore this analysis should inform decision makers when considering prevention and control policies of IPD but also other forms of CABM and further research.

Is pneumococcal meningitis a good surrogate for assuming these results to other forms of CABM? Pneumococcal meningitis is one of the most common causative forms of CABM in adults, particularly so in countries with Hib and Men C conjugate vaccination programmes. Clinical features are not distinctly different from other causative forms of CABM, hence diagnosis / ascertainment should not be significantly different. It is possible as elaborated earlier that blood testing is used when a LP should have had been done, leading to a diagnosis of IPD rather then meningitis specifically. However,

this - i.e. a decreasing trend of LPs performed was not shown in my validation exercise in the SW region. If it does happen, that is if blood tests are used over the CSF tests, it should be similarly extended to all forms of CABM, as it is shown with epidemiological data in the trends of meningococcal meningitis vs meningococcal septicaemia. Lastly there are no reasons why reporting of pneumococcal meningitis should be different from other forms of CABM.

Modelling studies into Pneumococcal Conjugate Vaccine (Melegaro and Edmunds 2004; Melegaro and Edmunds 2004) reported that rather than targeting high risk groups, vaccination policies for adults are most cost-effective if implemented for all persons above 65 years. Evaluation of the pneumococcal conjugate vaccine (PCV) based on data from the Kaiser Permanente trial indicate that population based programmes for infants and children are cost-effective compared to PPV, or no vaccination (Black, Lieu et al. 2000; Lieu, Ray et al. 2000). Data from England and Wales show that the 7 valent PCV has about 77% of serotype coverage in adults aged 65 and over and 51% in younger adults (George and Melegaro 2001; Sleeman, Knox et al. 2001). In the context of these revised estimates, the benefits of vaccination are likely to be greater then assumed, particularly in the over 85 year olds where the sensitivity of the data sources fell below 20%.

Do these revised estimates of the burden of pneumococcal disease amongst younger adults suggest consideration for vaccination at an earlier age? Despite the apparent high cost of vaccination (Ament, Baltussen et al. 2000), I suggest that a detailed cost-benefit analysis of PCV vaccination of adults across a range of different ages is required (Weycker, Richardson et al. 2000). This analysis should take into account my revised estimates for incidence and deaths, the efficacy of the new pneumococcal conjugate vaccine in a younger adult age group, the potential for immunological boosting by further vaccination in old age, the impact of herd immunity, and the potential for a decrease in the carriage of antibiotic resistant strains (Black, Lieu et al. 2000) (Dagan, Givon-Lavi et

al. 2002; Kyaw, Lynfield et al. 2006). Also, the costs saved due to averted cases should be taken into account, including indirect costs associated with reduced work loss, or averted future productivity loss due to disability or death caused by IPD.

Whereas efficacy of Pneumococcal Polysaccharide Vaccine in the elderly has been reported to range between 45 to 68% (Foster, Knox et al. 2008), (Sankilampi H, Pekka Honkannen P et al. 1996),(Butler, Dowell et al. 1998), efficacy of the new Pneumococcal Conjugate Vaccine (PCV), as from its licensure (US 2000 and Europe 2001) in this population is still unknown (Parijs and Malinoski 2004). Data from the Kaiser Permanente Pneumococcal conjugate Efficacy Trial report an 78% efficacy of PCV in infants (Black, Shinefield et al. 2000). In the cost-effectiveness analysis from the trial the authors report that vaccination can be even cost-saving for the health care perspective at a reduced cost per vaccine dose or if incidence of disease is higher (Lieu, Ray et al. 2000), (Hueston, Mainous et al. 2000), (Le 2000). Results from this study, reporting almost double of incidence and fatality then reported from routine data sources, and taking account that the cost of the vaccine has now dropped, show that the efficacy of the PCV is likely to be higher than previously thought. However, the use of the PCV in children seems to be resulting in a decreased carriage of pneumococci, and indirectly having an effect in reduced IPD amongst adults (George, Pauline Kaye et al. 2008). This effect has been shown with other conjugate vaccines, i.e. Hib and MenC (McVernon, Howard et al. 2004; Trotter, McVernon et al. 2008).

The presented results (in Chapter 5) should inform policy making with regard to pneumococcal vaccination policies in adult but also to the management of meningitis amongst adults –as will provide information on the likelihood of a pneumoccoccal meningitis occurring, as opposed to another form of CABM (and the appropriate treatment, and specifically antibiotics, depend on the different causative organisms). When considering policies and strategies for prevention, such as vaccination, data

showing that the burden of the disease is likely to be twice as high, has a significant impact, eg on the cost-benefit analysis.

8.4.4 The impact of the PCV 7 on the epidemiology of pneumococcal meningitis, and IPD, so far

In 2002 PCV7 was recommended for use in at-risk children under 5 years of age in the UK. From September 2006 PCV7 was introduced into the routine childhood immunisation programme. PCV7 contains the serotypes 14 , 18C , 19F , 23F , 4, 6B , 9V.

The Health Protection Agency (HPA) monitors the impact of the programme through the enhanced surveillance for IPD and by actively following up every case of IPD in England, Wales and Northern Ireland, in children eligible for vaccination.

Since the introduction of PCV7 in England and Wales there has been a marked reduction in the rate of cumulative increase of cases of disease caused by the vaccine serotypes some herd immunity in older age groups. Similar benefits are reported from elsewhere (Grijalva, Nuorti et al. 2007; Isaacman, McIntosh, Reinert. 2009). However, the incidence of disease due to non-vaccine serotypes appears to have been increasing and serotype replacement is a concern (ref Kaye, ###).

Higher valency vaccines, such as PCV10 and PCV13 appear to offer modest benefits in terms of costs saved and QALYs gained compared to PCV7. However, evidence of replacement disease caused by serotypes not in either of these two new conjugate vaccines is occurring. (ref: Kaye, Malkani *et al.* 2009)

Changing characteristics of IPD after the introduction of the PCV7 have been reported from other countries, as well. For eg in Atlanta, US the rates of non-PCV7 serotypes increased in both children and adults in the four year period following the introduction of the PCV7 (2000-2004) (ref Albrich, Baughman *et al.* 2007). However, considerable and significant changes in the serogroup distribution of *S. pneumoniae* over time in the

period preceding the introduction of PCV7 we reported. (ref: Jefferies, Smith *et al* .2000; Foster, Knox, et al.2008).

A study using the inpatient data for US (the Nationwide Inpatient Sample) during a ten year period 1994 to 2004 estimated the national trends in the rates of hospitalization for pneumococcal meningitis before and after the introduction of the PCV7 in 2000. It reported a significant decrease in annual rates of hospitalisations of 50% among children 2-4years and 33% amongst adults >=65 years. Other studies reported similar results (Ref Tsai, Griffin, *et al.* 2008; Albrich, Baughman *et al.* 2007). These findigs are further strengthened with a recent study that examined trends in pneumococcal meningitis in the US comparing the causation by PCV7 serotypes, and non-PCV7 serotypes. The authors examined changes in the incidence of pneumococcal meningitis from the introduction of the PCV7 in 2000 comparing to the baseline values from 1998–1999. They reported that rates of pneumococcal meningitis have decreased among children and adults since PCV7 was introduced. However, an associated increase in meningitis caused by non-PCV7 serotypes was also reported and highlighted as a concern. (Hsu, Shutt et al. 2009)

Apart from a decreasing number of cases of the invasive disease, an indirect effect on the carriage of the vaccine serotypes amongst the household members of a PCV7 vacinee is reported. (ref: Millar, Watt *et al.* 2008; Kaye, Andrews *et al.* 2008). Nonethelss, ultimately the most cost efficient prevention would be a vaccine that would have the ability to protect against invasive disease independent of serotype (Barocchi, Censini, Rappuoli 2007).

8.5 Does this review of clinical management provide opportunity for improving clinical practice?

8.5.1 Overview

The findings from the review of the medical notes emphasise a few important issues with regard to the potential for improved clinical management:

- that these potentially devastating conditions are not commonly seen in a hospital setting (median 8 adult cases per year per NHS trust)
- that suggested standards of care are not widely achieved, demonstrating a strikingly variation in medical practice between hospitals.

This research showed that in the context of potentially critically ill patients with serious infections, clinical records frequently do not contain essential information required for optimal patient management. Recently, considerable concern was expressed that paper-based patient record systems in the UK have no structure, are inconsistent and show no uniformity (Audit Commission 1995; Mann and Williams 2003; Huston 2004). As reaction to these concerns the Health Informatics Unit of the Royal College of Physicians (RCP) published in 2007 the "Generic medical record keeping standards" recommending use of a standardised proforma, with specific focus on most of the key standards which in my study were found to be of poor record keeping (Carpenter, Bridgelal et al. 2007). Importantly, this study showed an aparent variation between NHS healthcare trusts, where recommended standards of clinical practice in some areas were met in 0% of cases in some trusts and 100% in others. Although in most elements of management this variation did not reach statistical significance, the magnitude of the differences suggest the potential for improvement and indicates that several key steps in the management process should be amenable to interventions aiming to narrow this variation (Sterne JA, DaveySmith G 2001).

8.5.2 Making a diagnosis

Previous reports have suggested that when faced with a febrile patient with no apparent focus of infection, general practitioners place less importance on making a definitive diagnosis than discriminating between self-limiting and potentially serious illness (Granier, Brennan). It was therefore not surprising that among those patients seen by a GP prior to hospital admission in my cohort, a differential diagnosis of CABM or MS was recorded in less than half of cases. However, once a patient reaches hospital, early recognition is essential to guide appropriate intervention (Heyderman, Lambert et al. 2003).

Diagnosis at arrival was recorded in just over the third of case-records, and the actual diagnosis ranged from 'fever' or 'confusion' to 'malaria', or even 'strange' in one case. Most of the records did not have a diagnosis specified at arrival at all (37%).

In this retrospective review I found that only three-quarters of patients with CABM or MS were assessed within one hour of arrival and that there was (clinically large but statistically not significant) variation between hospitals. More than a quarter of patients did not have an appropriate differential diagnosis at this assessment. The clinical features of CABM or MS in the early stages are often nonspecific and a high index of suspicion is needed to distinguish them from the many febrile illnesses observed in primary care and emergency departments (Heyderman and Klein 2000). Nonetheless, this data suggests that diagnostic awareness needs to be strengthened in adult practice.

8.5.3 Initiating treatment

As anticipated from previous studies (Cartwright K 1992; Strang and Pugh 1992) and the difficulties identified by GPs in implementing advice regarding pre-hospital penicillin (Brennan, Somerset et al. 2003), parenteral antibiotics were given to less than the quarter of patients seen by a GP. Patients with CABM or MS may appear relatively well at presentation but may deteriorate rapidly without warning. In hospital, therefore,

stabilisation and institution of specific therapeutic measures are crucial to patient management (Begg; Heyderman, 2003). I found that close to a quarter of the cases did not receive antibiotics within 1 hour of first assessment (range 0 to 2 days). In this review I did not specifically assess the reasons for this delay but I found that when a diagnosis of CABM or MS had been made, initiation of antibiotic treatment was more likely. Whether there were delays while awaiting investigations such as LP or CT brain is uncertain (Aronin, Peduzzi et al. 1998; Miner, Heegaard et al. 2001; van De Beek, de Gans et al. 2002). The role of LPs goes beyond management of individual patient; it contributes to the appropriate prophylaxis of contacts, possible outbreak detection, surveillance and programme evaluation (Clark, Duffell et al. 2005).

8.5.4 Assessment of severity and review by a senior staff

In any patient with CABM or MS a severity assessment should be made, documenting any warning signs of shock or raised intracranial pressure so that an appropriate continuous management can be sustained (Heyderman 2003). Senior input into the management of such patients is required early, in some of the specialties, such as respiratory medicine it is required that a consultant assesses the patient in no less then 12 hours. In this review of clinical management, I found that a severity assessment was done for just over half of the cases in the entire cohort and significantly less CABM cases were assessed for severity as compared to MS cases. Although these findings may reflect poor record keeping, other studies have demonstrated that the standard of care received by acutely ill general medical inpatients in the UK is not optimal {Report of a Working Party of the Royal College of Physicians, 2002}. Indeed one confidential inquiry suggested that more than 50% of critically ill patients receive suboptimal treatment prior to admission to intensive care (McQuillan, 1998). The considerable variation in severity assessment observed between hospitals could be explained by unsuitable organisation, infrastructure or clinical leadership and governance, but also highly likely due to a lack of appropriate clinical training and supervision of junior staff.

Most patients were assessed first by junior medical staff, only half were reviewed by a supervising consultant within 12 hours and some patients were not seen for more than 2 days. Also, I found that LP continues to be undertaken were there is clear evidence of raised intracranial pressure or cardiovascular compromise (Clark, Duffell et al. 2005). Conversely, despite an emerging consensus that brain CT does not rule raised intracranial pressure and should not be part of the initial routine management of CABM (Heyderman, Lambert et al. 2003), CT brain was undertaken in over half of the cases. A recent report of a working party of the Royal College of Physicians recommended that that every new patient admitted should be reviewed by a consultant physician within 24 hours (Royal College Physicians 2004). Depending on whether MS or CABM predominates, the major clinical management problems may differ considerably. Decisions on which and when interventions should be performed can be extremely difficult and such decisions require early senior input and involvement of the critical care team. Amongst the severely ill patients in this review, the median time for assessment by a critical care team was more than 2 hours. These results show that in only one case a consultant was involved in first assessment of the patient and only half of cases were seen by an ICU team at any stage, suggesting that there is a lack of senior or critical care assessment, which may be associated with a worse outcome (Booy, Habibi et al. 2001; Ninis, Phillips et al. 2005), underlining the importance of such review.

8.5.5 Prevention and public health management

National guidance (Public Health Laboratory Service, Public Health Medicine Environmental Group et al. 2002) recommends that that prophylaxis should be initiated in all probable cases of MS or CABM, yet a significant number were not notified and prophylaxis to index case was not done for all cases. The severity of meningococcal disease and its tendency to occur in clusters, particularly among the household contacts of an index patient, necessitates notification of the consultant for disease control and antibiotic prophylaxis for close contacts and the index case (Purcell, Samuelsson et al.

2004). These findings underscore an inadequate interface between hospital and public health services.

8.6 Can clinical management change the outcome of CABM and MS?

There has been much debate in recent years around the importance and, effectively, the benefit of the recommendations for an early and prompt diagnosis and management of meningitis (Talan, Hoffman et al. 1988; Meadow, Lantos et al. 1993; Wilks and Lever 1996; Hahne, Charlett et al. 2006).

Some studies have found an association between the delay in initiation of antibiotics with an adverse clinical outcome. However, generally the authors of these studies have also reported that it has been difficult to be differentiate between the effect of antibiotics in the outcome of illness from the effect of severity of illness and other prognostic factors, such might be co-morbidities (Aronin, Peduzzi et al. 1998). Surrogates of antibiotic delay (for example, duration of symptoms before admission to hospital and time to sterilization of cerebrospinal fluid) have been associated with adverse outcome in some studies, but no study has identified delay in initiation of antibiotic therapy as an independent risk factor after adjustment for other variables that affect clinical outcome (Kilpi, Anttila et al. 1993; Quagliarello and Scheld 1997).

A study that examined *whether antibiotic timing influences* clinical outcome of patients with CABM concluded that for patients with the highest level of clinical severity, the risk for adverse outcome is influenced more by the severity of illness than the timing of initial antibiotic therapy (Aronin, Peduzzi et al. 1998). Another recent study focusing on children suggested that patients who were administrated parenteral antibiotics before hospital admission had more severe disease and poorer outcomes then those who were not given penicillin before admission (Thomspon, Ninis, 2006). However the authors did also recognise that the association with adverse outcome may have been because children who are more severely ill are being given penicillin before admission.

I did not find an association between clinical management and outcome of CABM and MS. The results of the univariate analysis, and then the multivariable logistic regression of those factors significant in the univariate analysis, indicated the association of adverse outcome with a few key outcome predictors, including demographics, clinical and laboratory features, very much in line with previous reports (Durand, Calderwood et al. 1993; Grimwood, Nolan et al. 1996; Laurichesse, Romaszko et al. 2001; Short and Tunkel 2001; Meyer, Samuelsson et al. 2004; van de Beek, de Gans et al. 2004). Uni or Multivariable analysis examining the key clinical indicators with the outcome (i. adverse – including death or long-term sequelae; ii. good – recovery) and controlling for the effect of the clinical predictors that were significant in the multivariable logistic regression did not, reach statistical significance except for diagnosis witin one hour which showed a protective effect in univariable anaysis. I discussed the limitations for this part of the research and the alternative statistical methods that might have had been employed in the Discussion section of Chapter 7 and as a recap the main limitations were:

i. Study was not designed to test such a hypothesis (i.e. a null hypothesis that clinical management has no effect on the outcome of the disease);

ii. The relatively small number in the study sample, particularly the number of patients with adverse outcome

iii. The missing data for both, the timing of the clinical indicators performed and indicators of severity of illness.

I discussed in Chapter 7 the limitations of my study in examining the association of clinical management with the outcome of CABM and MS and approaches to overcoming them e.g. dealing with missing data. I attempted to stratify the patients based on their severity of illness on arrival before the administration of the antibiotics, in order to then examine the association per each group, however the data on severity were lacking. This was owing to incomplete record keeping but also due to fact that they were not collected in a way to support examination of such associations, as I had not included this

examination when I designed the study (either the study power or the questionnaire for data collection.

8.7 Strengths and limitations of this research

In the sections below (8.7.1 and 8.7.2) I will emphasize the overall strengths and the briefly the overall weaknesses of the research. I have discussed the specific limitations of each part of my research within the respective chapters (Chapter 4 to Chapter 7).

8.7.1 Strengths

This research provides the first nationally representative examination of the epidemiology and clinical practice in relation to CABM and MS in adults in England and Wales. I have used different, research approaches for the appropriate parts of this research. E.g. to examine the epidemiology I used the available routine surveillance data, that are nationally representative and accredited, undertook comprehensive and robust analysis for incidence, mortality and case-fatality rates. I compared the analysis employing Poisson regression models with Binomial regression models to account for overdispersion of surveillance data. Further I undertook a regional exercise, in which I was able to obtain straight from the source of reporting, i.e. the local microbiological laboratories, the number of CSFs tested during the study period.

I then applied statistical approaches to examining their accuracy and providing improved estimates. The capture-recapture analysis is widely used and recognised as an improvement of disease estimates as compared to those from routine data. I applied a rigorous analysis for incidence and mortality, and also several approaches to sensitivity analysis, including: definition of matched cases, inclusion of all diagnostic fields, calendar year vs financial yea period, etc.

The review of clinical management of CABM and MS is the first national study to review comprehensively pre-hospital and more thoroughly hospital diagnosis, first and continuous assessment and management, both clinical and public health, of adult cases. I reviewed over 20 cases (over 260 including the cases form the pilot study) and had a nationally representative sample of both hospital trust and actual cases. I myself

designed the questionnaire and collected the data throughout- ensuring this way a high reliability, validity and consistency in the data collected and the process. The study was overseen by a panel of national experts in various relevant fields, including: epidemiology, immunology, microbiology, general practice, paediatrics and geriatrics, intensive/critical care, statistics, etc. I undertook robust and comprehensive statistical analysis and in addition considered the benefit and appropriateness of more advanced analysis (e.g. multilevel modelling). Also the interpretation of the results is appropriately contextualised in view of other research.

The examination of clinical practice with the outcome of disease (i.e. CABM and MS in adults). Is a step further to expand the and explore the ways to reduce the burden – it aimed to provide information on the actual impact of clinical guidelines and the ultimate benefit to the patients outcome with an improved clinical practice. I examined the key indicators of clinical practice, developed appropriate techniques and steps to ensuring a robust statistical analysis, including definitions of inclusion criteria, patients characteristics – demographics, causation, co-morbidities and clinical and microbiological components – to achieve an effective was of dealing with the confounding into the effect of actual clinical management in outcome. However, as discussed in the limitations in Chapter 7 and will be briefly addressed below – owing to two principal issues, i.e. the design of the study and non-availability of data in medical records, much of this analysis did not reveal statistically significant results

Weaknesess

I have addressed in specific the weaknesess of each part of my research within the espective chapters (Chapter 4 to 7). The quality and scarseness of data overall showed to be the greatest weakness of this research, and that being either the routine epidemiological data or clinical mdecial records.

A prospective clinical management review study would have had provided more information on the clinical practice and possibly overcome some of the issues with

missing data, however this design is known to introduce bias to the normal clinical practice – i.e. the awareness of clinicians that are part of the research in itself improves clinical practice.

Limitations specific to the data and methods related to the Chapter presented are included in the Discussion sections within each relevant chapter (ie chapters 4 to 7).

Chapter 9

Conclusion, recommendations and further work

Table of Content

9.1 Introduction

In this last chapter of my thesis I will set out my conclusions from this research, drawing together all the aspects examined along with the results of the data and their interpretation.

I will then present my recommendations resulting from this research, joining the aspects of the epidemiology and clinical management, then going into details of my recommendations for improving the clinical practice (that I had prepared for the DH when reporting the findings of the review of clinical management).

Lastly I discuss how can this research be taken further and what are the further interesting avenues that my work warrants.

9.2 Conclusion

Knowing the epidemiology of a disease, in this case CABM and MS, is crucial for following trends, detecting changes, e.g. outbreaks, developing appropriate prevention strategies, and also for increasing the potential of improved knowledge and hence clinical management, as well. The data I presented in this thesis underlines the importance of maintaining a high index of clinical suspicion for CABM and MS, with a heightened focus amongst the elderly where the diagnosis has previously been considered unlikely in this age group. When a clinician has a better understanding regarding how likely it is that an adult presents with CABM or MS, what sort of causative organisms are common on which age groups, and what the variations are in the geography of distribution – they are more likely to instigate appropriate diagnostic procedures and treatment. My research has provided an understanding of the epidemiology, previously, until my findings were disseminated, relatively unknown and unrecognised.

Measuring the extent of the underreporting also provided a contribution to the understanding of the epidemiology and opportunity for the prevention strategies to more

appropriately address the disease in adults. The results of my capture-recapture analysis showed that cases of and deaths from pneumococcal meningitis among adults are almost twice of those routinely reported, finding this largely in line with other studies in similar conditions countries (Faustini, Fano et al. 2000) (Trotter, Samuelsson et al. 2005)., across Europe. This study adds to the evidence on bacterial meningitis in the adult population. Even though it is not disputed that attention should be in under 5s where most of disease occurs, these results suggest that more attention should be paid to diagnosing meningitis in adults.

Underreporting of other forms of CABM has been reported by numerous studies and across different countries (Faustini, Fano et al. 2000) (Trotter, Samuelsson et al. 2005). The recording practices in HES, laboratory reports or ONS are not suspected to vary significantly between different forms of CABM. This will also was in part addressed in Chapter 7, reviewing the hospital records of patients with CABM I found that the information recorded in medical notes and the notification off cases (meningococcal disease in specific) to the CCDC was often and indiscriminative to the causative organism inappropriate.

I further reviewed the clinical management of adult cases with CABM and MS in hospital setting across England and Wales. The sample was a random selection of hospitals and cases (where appropriate). Measuring the clinical practice against recommended standards provided the opportunity to identify the suboptimal practice and address – both – the actual clinical practice and the ways of active dissemination of standards. However, once knowing the current standards of practice we need to show that clinical practice does actually, or at least has the potential, to improve the outcome of the cases. To address this I examined the association of clinical practice with the outcome, data presented in Chapter 7. Although preliminary results showed to be in the direction of a protective effect of the recommended standards of care (e.g. review within 1hr), the study lacked the power to detect marginal changes with a statistical significance; and the

missing data added an obstacle to properly examining this association. This arose largely as the study was not designed to address this question - it was designed with power to only measure clinical practice against recommended standards, and the data collection was done with focus of measuring clinical standard, rather then providing opportunity for examining association. I.e. data collected needed to be as representative of the current practice at the time and not introduce a non-realistic situation, e.g. by going further to collect the data that was not available in the medical records of the patient.

9.3 General recommendations and further research

The examination of the epidemiology of CABM and MS in England and Wales during 1991 to 2002 showed a changing epidemiology, with different changes occurring for the causative organisms, a shifting burden of the disease towards the older ages. It is likely that since when I carried out the study, i.e. up to 2002, the epidemiology has changed further, overall incidence probably decreasing significantly, due to the decrease in Hib and Men C meningitis / MS following the respective conjugate vaccination programmes. Bacterial meningitis (assuming CABM and MS) has become a more rare disease, however, as it is a predominantly a childhood disease, it will require caution to assume that the decrease in childhood has been mirrored into the adult disease, even though my data seemed to suggest that that might have been happening. E.g., the increase in incidence in Hib meningitis in the early 2000s calls for a cautions approach to assuming a decrease of the burden of the disease. The capture-recapture results showed that the *actual burden of pneumococcal meningitis*, and possibly similar results for other forms of CABM, is likely to be twice as high of what reported through routine surveillance. *The* data from the review of clinical management , though of different nature and objective, supported much of the revelations regarding the epidemiology, e.g. with regard to the causative factors, issues with ascertainment and reporting (late or no reporting of cases to the CCDCs) as well as the case-fatality rate of the disease. Hence – a continuous

examination of the epidemiology, accounting for the rate of under-ascertainment / under-reporting, is necessary for an effective control of this vastly preventable condition. In the last few years the pneumococcal conjugate vaccine (PCV) has been also introduced to the childhood immunisation programme. I recommend that a detailed examination of the epidemiology of the disease in adults is carried out – now ten years since the introduction of the Men C vaccine; then, partially depending on the results of such a review - cost-effectiveness analysis for extending the conjugate vaccination programmes to adults at risk, e.g. the PCV to over 65s, should be carried out. The immunologic studies into mucosal immunity for *Neisseria* and pneumococcus could be linked to the examination of the epidemiology as potentially would provide data to validate / compliment the routine surveillance data.

My review of clinical management of CABM and MS amongst adults in England and Wales demonstrates a need for improvement in several areas of clinical practice relating to CABM and MS. Central to an improvement in adult practice should be better recording of essential clinical information, further training in the diagnosis, severity assessment and management of acutely ill patients with serious infections and improved senior /specialist supervision. Specific guidance should be given on documentation of disease severity which could be incorporated into a standard generic clerking proforma. Patients with suspected CABM should be reviewed promptly on arrival and parenteral antibiotics should usually be given as part of the first assessment. Severely ill patients should be reviewed rapidly by a supervising consultant or critical care specialist. Competency in the necessary core skills should be assessed and become a mandatory requirement for progression through the new foundation training years in the UK. In addition, the management of critically ill patient with an infection should be included in the undergraduate curriculum. Consensus guidelines on management of these conditions should be promoted using interventions that effectively improve compliance. A repeat review to complete the audit cycle is an essential element of clinical

governance in the NHS and should be undertaken to test the efficacy and uptake of the interventions put in place. To plan and facilitate change of the clinical practice the recommendations from NICE guidance on behaviour change published recently (NICE 2007) should be taken into account. This guidance is aimed at helping people, NHS professionals, policy makers, to change their health-related knowledge, attitudes and behaviour. The above listed recommendations have been addressed in specific in my recommendations to the DH when reporting the findings from the review of clinical management, presented in Appendix 6.

It is important to measure the effect of the clinical management into the outcome of the disease. Some of the above recommendation, particularly to do with the record keeping, should facilitate such an undertaking. However, a properly designed and conducted study that would be sufficiently powered to detect a potential association of the clinical management with outcome and appropriately accounting for potential confounders, the major one being the severity of the disease, should be considered. This study could be as part of a repeat cycle of review of the clinical management and cost-effectiveness studies for effective prevention strategies, i.e. vaccination. This research could be linked to my research presented here, and draw from the initiatives that have followed the research into management of childhood meningitis (MRF funded research) i.e. production of training materials or management of paediatric meningitis. The DH should consider funding a repeat review to complete the audit cycle and MRF might have funding to complement this study with provisions for training materials. I have been considering a proposal for a further research that draws from my findings presented in this thesis, which though in an embryonic form indicates some further avenues to improve our knowledge for more effective control – reduction of the burden, of CABM and MS in adults in England and Wales. A copy of this draft proposal is shown in Appendix 7.

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Appendicies

Appendix 1

The original proposal to the Department of Health, 2001: "Community Acquired Bacterial Meningitis and Meningococcal Septicaemia in Adults: A Review of Diagnosis and Management"

Background

Bacterial meningitis and meningococcal septicaemia are important causes of preventable morbidity and mortality in the UK. Around 900 cases of adult bacterial meningitis are reported each year, primarily caused by Neisseria meningitidis and Streptococcus pneumoniae. In addition, almost 500 adult cases of meningococcal septicaemia without meningitis are reported annually. The introduction of a meningococcal serogroup C vaccine to the national immunisation programme has had a dramatic impact on the number of cases of serogroup C disease N. meningitidis in the UK [1, 2]. However, serogroup B strains are the commonest cause of bacterial meningitis and the annual numbers serogroup B-related cases of meningococcal septicaemia have been rising recently (PHLS data). Serogroup C vaccines do not protect against serogroup B disease and a specific vaccine is unlikely to be widely available for at least five years. Although conjugate pneumococcal vaccines appear potent in children [3], their efficacy in preventing meningitis in older adults is unproven. Clinicians and public health physicians will therefore need to remain vigilant for the possibility of cases of meningitis and septicaemia.

Potential improvements in the way we identify and manage patients who may have meningitis or septicaemia have been identified for all levels of healthcare [4]. These range from parental awareness through to the interface with primary care and emergency departments to the management by specialist paediatricians and physicians

[5-9]. Such studies have focused largely on meningitis and septicaemia in childhood (the majority of cases), have resulted in significant improvements in our approach to suspected paediatric cases and have been associated with a reduction in mortality, particularly amongst septicaemic cases in this age group [10].

Adult meningitis and septicaemia have been less well studied. The mortality amongst otherwise fit young adults remains higher than amongst younger children [4]. Clinical management varies considerably between centres. Data emerging from a recent prospective study conducted by the Royal College of Paediatrics and Child Health, suggests that there are marked deficiencies in health care delivery to adults with bacterial meningitis or meningococcal septicaemia (Dr N Nennis, personal communication).

In paediatric practice, the formulation of widely accepted management algorithms, targeted postgraduate training and a greater willingness to refer critically ill patients to specialist centres has had a significant impact on the morbidity and mortality associated with bacterial meningitis and meningococcal septicaemia in this age group [11]. To address this issue the British Infection Society (BIS) published guidelines in 1999 for the management of acute bacterial meningitis in immunocompetent adults [12]. The failure to integrate such guidelines and the CMO's national recommendations into everyday clinical practice is of considerable concern. Before the barriers to implementing good practice in the management of adults with bacterial meningitis and meningococcal septicaemia can be identified and addressed, it is essential to establish the nature and the size of the problem. The proposed study will assess the extent to which current practice in the acute management of these conditions meets the standards set by the BIS guidelines, focusing specifically on delays in diagnosis and administration of

antibiotics, appropriate use of monitoring, investigations, intensive care facilities and management of the complications of the disease, primarily shock.

This proposal will establish collaboration between academic microbiology, epidemiology, public health medicine, primary care, general internal medicine and infectious diseases. This will bring together the specific skills and experience necessary to generate outputs that will identify problem areas, inform policy, lead to specific recommendations and identify mechanisms that will enable clinicians to implement best practice. This study has the potential to lead to a significant reduction in the morbidity and mortality associated with bacterial meningitis and meningococcal septicaemia across the United Kingdom.

Aims and Objectives

This project will establish the extent to which current management of community acquired bacterial meningitis and meningococcal septicaemia amongst adults meets the standards set by the British Infection Society and the CMO. We plan to address the following specific aims:

1. To improve current estimates of the incidence and mortality associated with acute bacterial meningitis and meningococcal septicaemia.

2. To conduct a retrospective review of current diagnosis and management of adults presenting to randomly selected acute healthcare trusts, focusing on BIS standards and recording other outcome measures including morbidity, mortality and length of hospital stay.

3. To identify key areas of deficiency in current management of bacterial meningitis and meningococcal septicaemia in adults.

4. To generate further specific recommendations to improve clinical management.

Plan of Investigation and Methods

1) EPIDEMIOLOGICAL REVIEW

A further review of the literature will be conducted to establish historical estimates for the incidence and mortality associated with bacterial meningitis and septicaemia in adults. These estimates will then be compared with current data derived from the Public Health Laboratory Service, statutory notifications of infectious diseases, HES data, enhanced surveillance, data from consultants for communicable disease control (CCDC) and the RCPCH meningococcal study.

2) STANDARDS FOR BEST PRACTICE

The BIS and CMO's guidelines will be reviewed by an expert panel in the light of the current literature. The panel will consist of at least one of the following: a microbiologist, an infectious diseases physician, a public health physician, an epidemiologist, a general practitioner, a general physician and a physician specialising in care of the elderly (see appendix II). Standards will be identified relating to pre-hospital management, early in-patient management and investigation, and completeness of recording of information. Specific emphasis will be placed on factors leading to delays in diagnosis and administration of antibiotics, early identification of at-risk individuals, appropriate use of investigations, use of intensive care, and management of the complications of the disease, primarily shock. Where possible, standards will be based on randomised trials or well-conducted clinical studies. These standards will also be reviewed by the research and development division of the DH. The standards will be further modified on the basis of the initial pilot phase of the study (see below).

3) SAMPLING METHOD FOR THE CLINICAL MANAGEMENT REVIEW

Data will be collected by a retrospective case-note review. Although a prospective study may yield more reliable and comprehensive data in some areas, there is insufficient time

to establish a research network for such a study, and the use of sentinel centres for such a study would inevitably introduce an acquisition bias. Approval from the PHLS research ethics committee and the multi-centre research ethics committee (MREC) will be obtained before commencing the sampling. Acute healthcare *trusts will be surveyed* using a random cluster sampling technique [13]. This should ensure that the sample includes patients admitted to a range of specialist, non-specialist and district general hospitals, and across a variety of regions. The data should therefore be generalisable. All potential cases of adult meningitis and meningococcal septicaemia presenting in the previous year to these trusts will be identified through hospital data, laboratory records and CCDC data. An on-site case note review will then be conducted of all cases ≥16 years of age with acute community acquired bacterial meningitis (either a compatible CSF or microbiologically proven) and/or meningococcal septicaemia (characteristic rash or microbiologically proven). Individuals who have undergone recent neurosurgery, with recurrent meningitis or who are significantly immunocompromised will be excluded.

4) REVIEW OF CLINICAL MANAGEMENT

The case note review will be carried out by a clinical research fellow who will compare management and investigation with the study standards, using a survey instrument developed by the expert panel (see appendix I for draft version). Disease severity for meningitis and meningococcal septicaemia will be recorded using standard parameters [4, 14-16]. Data will be collected to establish the specialist/ non-specialist nature of the unit where management took place, the length of hospital stay, morbidity (deafness, neurological deficit, skin or limb loss) and mortality. The accuracy and completeness of the clinical note taking will be assessed by cross-referencing the charts, the medical and nursing records. The review will be conducted in two phases, firstly a pilot study (4 healthcare trusts) to evaluate the utility of the study instrument, to assess the reliability

and completeness of the study data, and to refine the review process; and then secondly, using methodology modified on the basis of our initial findings, a full-scale survey (20 healthcare trusts). It is estimated that between 10-15 cases will be identified at each healthcare trust. Therefore, between 40-60 cases will be reviewed in the pilot study and 200-300 cases will be available for the full analysis. However, the sample frame for the full-scale survey will be adjusted on the basis of the data derived from the epidemiological review and pilot study. In paediatric practice, there is a strong impression, based on some preliminary data, that the move to refer critically ill patients to specialist centres or units has had a significant impact on the morbidity and mortality associated with bacterial meningitis and meningococcal septicaemia [11]. We propose to explore this possibility in adult patients using data derived from specialist vs non-specialist units. Based on the observation that up to 70% of individuals receive sub-optimal treatment in hospital [8], this study would be able to detect a 20% difference between specialist and non-specialist units with 85% power at a significance level of 0.05. While it is appreciated that it is likely that more severe patients are admitted to specialist units, differences have been observed in the paediatric setting despite this confounder.

5) DATA STORAGE

Study patients will be assigned an anonymous study code and the data will then be entered onto a password-protected computer database for analysis. Information on each sample site will be retained but individual named hospital or trust data will not be disseminated without permission.

6) DATA REVIEW, DISSEMINATION AND PUBLICATION

The pilot study data will be reviewed by the expert panel and the study instrument then modified prior to the main survey. The full-scale study data will be analysed using the

Mann Whitney-U test for continuous variables and the chi-squared test or Fischer's exact test as appropriate for discrete variables. Using the data collected, incidence and mortality rates will be calculated. Differences between specialist and non-specialist units will be determined. The relationship between sub-optimal treatment and length of stay will be assessed. While mortality data will be collected, the sample size will be too small to make comparisons based on this end point. The analysed data will be reviewed by the expert panel and formulated for presentation and publication.

A preliminary report based on the pilot data will be made to the Chief Medical Officer for dissemination in summary form rather than in detail. The details of the full-scale study will be made available to the Chief Medical Officer prior to submission for publication or disclosure.

Research Outputs

A number of specific outputs in relation to adult meningitis and meningococcal septicaemia will arise from this project. In addition to providing operational information that will enable us to optimise the main study, the pilot will generate a comprehensive epidemiological review and preliminary data on the use of existing guidelines and important departures from best clinical practice. The main study will establish a minimum data set describing current diagnostic and management practice; identify important departures from best clinical practice; and provide reliable data to inform policy and base practical guidelines to enable both primary and secondary care clinicians to achieve best practice. These outputs will take the form of a report to the CMO, presentation and publication in peer reviewed scientific journals.

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Appendix 2

List of Expert Panel members – for the review of clinical management

Name	Title / Affiliation to the study	Address / Affiliation
Dr James Stuart	Regional Director Co-investigator	HPA South West
Dr Henry Prempeh	Consultant in Public Health Medicine	Forth Valley NHS Board
Dr Rob Heyderman	Professor of Infectious Diseases, Consultant Principal Investigator	Dept of Pathology & Microbiology, University of Bristol
Michael Jacobs	Infectious Disease Consultant	University College Hospital
Prof. Keith Cartwright	Professor of Microbiology Co-investigator	HPA South west
Prof. John Cohen	Professor of infections Disease (Consultant) and Dean of Medical School.	Imperial College, from 1 Feb 2003 University of Brighton
Dr Ardiana Gjini	Clinical Research Fellow / (from 1 Jan 2004 Specialist Registrar in Public Health).	Department of Pathology & Microbiology University of Bristol
Dr Nelly Nenis	Specialist Registrar in Paediatrics (later on Consultant Paediatrician) Research fellow for the children's study	St Mary's Hospital, London.
Andrew Whitehouse	Consultant Physician, Geriatrics	Birmingham NHS hospital trust
Tom Nichols	Statistician	PHLS Statistics Unit CDSC Colindale

Appendix 3

Confidential

"Community Acquired Acute Meningitis and Meningococcal Septicaemia in adults: An Audit of Diagnosis and Management"

Standards and indicators for assessing diagnosis and management of acute meningitis & meningosepticaemia based on recommendations by the British Infection Society

6/06/02

1. OUTSIDE HOSPITAL MANAGEMENT

- **Treatment:** Parenteral benzylpenicillin (1200mg). Iv or im route

Contraindication - anaphylaxis

1. a) % of those seen by GP and diagnosis suspected, who were given parenteral benzylpenicillin (1200mg) iv or im route*.

** Excluding those with recorded anaphylaxis.*

2. EARLY HOSPITAL MANAGEMENT

- **Assessment of severity of illness:** Severely ill patients managed in ICU/HDU

2. a) % of all patients, where differential diagnosis includes meningitis/meningosepticaemia, assessed by ICU team.

2. b) % of severity of illness assessed recorded.

2. c) % of severely ill* patients managed or referred to ICU/HDU.

- **Investigations**: CT or MRI to all patients with papilloedema or focal neurological signs.

2. e) % of patients with papilloedema or focal neurological signs who had CT or MRI scan.

- **Investigations**: appropriate blood and CSF diagnostic investigations in all suspected cases.

2. f) % Blood for Meningococcal culture

**severely ill patient: patient presenting with signs of meningeal irritation and impaired conscious level and/or petechial rash.*

2. g)

If predominantly septicaemia suspected

- % of Heart rate
- % of Respiratory rate
- % of Peripheral perfusion
- % of Blood pressure
- % of Urine output
- % of Mental status

If predominantly meningitis suspected

- % of Heart rate
- % of Respiratory rate
- % of Blood pressure
- % of Mental status (coma scale)
- % of Focal neurology
- % of Frequent seizures

% of Papilloedema

2. h) % Meningococcal PCR

2. i) % Throat swab for Meningococcal culture,

2. j) % Blood for Meningococcal serology.

2. k) % CSF for Meningococcal culture,

2. l) % CSF for Meningococcal PCR.

- **Lumbar puncture:** to all adult meningitis patients except when a contraindication

Contraindications: Clinical diagnosis of meningitis (Raised intracranial pressure) (ICP), focal neurological signs, severe shock, impaired conscious level, coagulation disorder, respiratory comprise or clinical diagnosis of meningococcal sepsis.*

**includes if Computer Tomography (CT or MRI) performed, shows raised ICP.*

2. l) % of meningitis patients who had LP

2.m) % who have LP in presence of contraindications.

- **Treatment/management**: IV antibiotics in less than 1 hour of admission* at hospital

** Time of the first assessment by medical staff (JHO, SHO, Registrar,..)at the hospital*

- 2.n) % of patients given IV antibiotics in less than 1 hour of diagnosis*.

** where diagnosis at arrival includes meningitis / meningococcal septicaemia.*

3. HOSPITAL MANAGEMENT:

- **Diagnosis**: The differential diagnosis should include meningitis/ meningococcal septicaemia at first assessment (< 12hrs).
- **Management**: Patient should be assessed by the consultant within 24 hours.

3.a) % with differential diagnosis of meningitis/ meningococcal septicaemia at first assessment (< 12hrs).

3.b) % of patients assessed by consultant within 24 hours.

- **Treatment of suspected meningitis or meningococcal septicaemia:**

Meningitis patients: Meningococcal patients:

3. c) % of cases with typical meningococcal (purpuric) rash given 2,4g benzylpenicillin iv or ceftriaxone or cefotaxime

3. d) % of cases without typical purpuric rash giv ceftriaxone or cefotaxime iv

3.e) % of suspected penicillin resistant pneumococcal meningitis* given 2g ceftriaxone or cefotaxime regime + 1g vancomycin or, 600mg rifampicin iv.

3. f) % of all case antibiotics administered intravenously throughout the treatment course.

**if within two months have had visited a high prevalent penicillin resistant country.*

4. NOTIFICATION AND PROPHYLAXIS

Notification: report to CCDC all clinically suspected cases

4. a) % of cases- reported to CCDC

4.b) % of cases reported within 24hrs of diagnosis, where diagnosis suspected.

- **Chemoprophylaxis to eliminate carriage:** Index cases should be given chemoprophylaxis before discharge from hospital

4.c) % of cases given chemoprophylaxis (rifampicin or ciprofloxacin orally), or ceftriaxone for eliminating carriage.

5. RECORDS

Records: All essential information* about the management of the case should be recorded.

5.a) % of essential information recorded.

5.b) % of results recorded from the investigations required.

**Essential information:: Assessment of vital signs (Pulse, Temp, Blood Pressure, Rash, Respiratory comprise); Assessment of meningeal signs (Neck stiffness,*

papilloedema, Neurologic Examination, conscious level, capillary refill time) at first Assessment. CSF investigations (opening pressure, WCC, WC differential, RBC, Gram stain, Proteins, Sugar, culture, Meningococcal PCR); Blood investigations [FBC (Hb, WCC, RCC, platelet count), CRP, PCR-meningococcal, sugar, clotting screen].

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2. Expert opinion, panel including: J. Stuart, K. Cartwright, J. Cohen, S Granier, R. Heyderman, M. Jacobs, T Nichols, N. Ninis, H. Prempeh, A. Whitehouse.

Appendix 4.

The study instrument (questionnaire) for data collection of review of clinical management (case-report form)

11/09/2002 ***Confidential***

Community Acquired Acute Meningitis and Meningococcal Septicaemia in adults: An Audit of Clinical Diagnosis and Management "
Instrument for the study

1) Hospital setting *Study no:*_____

Date of review: ___ / ___ / ___

Hospital code:_____ *Region code:* _____

Was the patient assessed or managed in:

Tick all that apply	Y / N / K
Accident & Emergency Dept	☐ ☐ ☐
Medical Assessment Unit?	☐ ☐ ☐
General medical ward?	☐ ☐ ☐
Infectious diseases ward?	☐ ☐ ☐
Neurology ward?	☐ ☐ ☐
HDU/ ICU?	☐ ☐ ☐
Paediatric ward?	☐ ☐ ☐

The main specialty of the consultant in charge of the patient: _____ (codes)

2) Patient Demographics

Age: _____ *Date of birth*: ___ /___ /___ (dd / mm / yy) Sex (*please circle as appropriate*): **M / F**

Recently visited country outside UK: **Y / N / NK**

If yes, specify the country:_____

3) Arrival at Hospital, Date: ___/___/___; Time:___:___

Did diagnoses on arrival include meningitis or meningococcal septicaemia: **Y / N / NK**

Is this a referral from another hospital: **Y / N / NK**

Death at Hospital **Y / N / NK** Date: ___/___/___; Time: ___:___

Transfer to other Hospital: **Y / N / NK** Date: ___/___/___; Time: ___:___

Discharge home: **Y / N / NK** Date: ___/___/___; Time: ___:___

HDU/ICU stay: From (date): ___/___/___, time: ___:___ ;

to ___/___/___, time: ___:___

4) Final Diagnosis

Bacterial meningitis? **Y / N / NK**

If YES

Clinical: **Y/ N / NK** Lab confirmed: **Y / N / NK** *(pls circle as appropriate)*

if Lab confirmed

Which organism isolated:1)_____2)_____3)_____ (codes 1-10)

TEXT BOUND INTO THE SPINE

Meningococcal septicaemia **Y / N / NK**

If YES

Clinical: **Y/ N NK** Lab confirmed: **Y / N** / NK

if Lab confirmed

Which organism isolated:1)_____2)_____3)_____ (codes 1-10)

5) Sequelae (recognised at discharge or at follow up)

	Y / N / K	*If **YES** describe:*
Deafness?	☐ ☐ ☐	_____(codes 1-3
Neurological deficit?	☐ ☐ ☐	_____
Severe scarring or plastic surgery?	☐ ☐ ☐	_____
Loss of digits or limbs?	☐ ☐ ☐	_____
Other, *please specify:* _____		_____

Was a hearing test done: **Y/ N/ NK;**

if YES: During Hospital stay

During first 4 weeks after discharge

Later

6) Pre-Hospital Management

Was the patient seen by a GP before admission to the hospital? **Y / N / NK**

If YES

Time when seen by GP for this episode, date: ___/___/___ , time:___:___

If referred to the hospital by the GP, time of referral, date: ___/___/___ , time:___:___

No of times seen by a GP for this episode: ☐

Did the GP observe a rash? **Y / N / NK**

Y / N / NK

Was *meningitis / meningosepticaemia* suspected by the GP? ☐☐☐

If YES

Was Benzylpenicillin given before admission? ☐☐☐

if **Yes** dose: _____mg ; route: _____

If NOT

Was the patient allergic to penicillin? ☐☐☐

If yes, was the allergy anaphlyaxis? ☐☐☐

Were oral antibiotics administered for this episode? ☐☐☐

7) Initial Hospital Assessment

First assessment*, Date: ___/___/___ ; Time: ___:___

**Time when first assessed by a medical staff (consultant, Registrar, SHO, JHO)*

Did the differential diagnosis include meningitis or meningococcal septicaemia at: first assessment **Y / N / NK**

If **Yes,** Date : ___/ ___/ ___ ; Time: ___: ___

First assessment made by: ☐ *(codes 1 -10)*

Did the consultant assessed the patient **Y / N / NK**

if **Yes,** Date: ___/___/___ ; Time:___:___

Did the ICU assessed the patient **Y / N / NK**

if **Yes**, Date: ___/___/___ Time: ___: ___

Vital signs Pulse _____/min

Temp _____C

Blood Pressure: Systolic: _____ mmHg ; Diastolic: _____ mmHg

Rash **Y / N / NK** *If YES:*

Non-haemorraghic ☐

Purpuric: ☐

Not known ☐

Rapid progressing rash **Y / N / NK**

Respiratory comprise

RR ____/min **NK** Cyanosis **Y / N / NK**

	Y / N / NK	
Convulsions >24hrs:	☐ ☐ ☐	*If YES: nature*_____
Neck stiffness	☐ ☐ ☐	
Papilloedema	☐ ☐ ☐	
Fundus examination done?	☐ ☐ ☐	
Neurological examination?	☐ ☐ ☐	
Focal nerve signs	☐ ☐ ☐	

Conscious level GCS score _____ **NK**

Shock Capillary refill time ____sec **NK**

Peripheral perfusion assessed: **Y / N / NK**

8) Management at the hospital

Did the antibiotic management include iv antibiotics within 1hr of addmission:

iv antibiotics: First dose Date: ___/___/___; Time: __ : ___

if NK

Given at first assessment: **Y / N / NK**

Name of the antibiotic: 1)_____Dose:_____mg ;Route:_____ (code 1or 2)

2)_____Dose:_____ mg ;Route:_____ (code 1or 2)

3)_____Dose:_____mg ;Route:_____ (code 1or 2)

I.V. antibiotics through out the treatment course **Y / N / NK**

Fluid management/ resuscitation plan recorded? **Y / N / NK**

9) Lumbar puncture

		Y / N / NK	
	Was a lumbar puncture performed?	☐☐☐	*if **YES*** date: ___/___/___*Time:* __
if Yes	Were antibiotics given first?	☐☐☐	
	Was a CT scan performed first?	☐☐☐	if **YES** raised ICP: **Y / N / NK**
if No	Where there specific contraindications	☐☐☐	*if **YES*** specify: _____(codes 1-5)

Were the following results requested:

	Y / N / NK	*If **YES*** record results:
CSF Opening Pressure	☐☐☐	_____
CSF WCC	☐☐☐	_____
CSF WC differential	☐☐☐	_____ *(predominant)*
CSF RBC	☐☐☐	_____
CSF Gram stain	☐☐☐	_____
CSF Protein	☐☐☐	_____
CSF Sugar	☐☐☐	_____
CSF PCR (meningococcal)	☐☐☐	_____
CSF culture	☐☐☐	_____

10) Investigations

Were the following investigations performed:

	Y / N / NK	*if **YES** give results:*
Throat swab?	☐☐☐	isolate:_____(codes 1-10
Scrapings or biopsy of skin lesions?	☐☐☐	isolate:_____
Blood Culture?	☐☐☐	isolate:_____

Were strains sent to reference laboratory **Y / N / NK**

Were the following investigations performed:

		Y / N / NK	*if **YES** give results:*
Meningococcal serology		☐☐☐	_____
CRP *(ESR or blood viscosity)*?		☐☐☐	_____
Blood PCR (meningococcal)?		☐☐☐	_____
pH blood		☐☐☐	_____
Urea		☐☐☐	_____
Chest X-Ray		☐☐☐	_____
Blood sugar		☐☐☐	_____
Blood gases		☐☐☐	_____
PH blood		☐☐☐	_____
pO_2		☐☐☐	_____
pCO_2		☐☐☐	_____
HCO_3		☐☐☐	_____
FBC:	Hb	☐☐☐	_____
	WCC	☐☐☐	_____
Clotting screen	APPT	☐☐☐	_____
		☐☐☐	

INR _____

Platelet count ☐☐☐ _____

Was the patient followed up as outpatient after discharge: **Y / N / NK**

if YES, for how long: _____ months;

which sequelae: _____

11) Management of contacts

Y / N / NK

Was the CCDC contacted ☐☐☐ if **YES** date:___/___/___Time: _

Prophylaxis to index case: ☐☐☐

if no, Ceftriaxone prescribed/given? ☐☐☐

12) Underlying Medical Condition:

Chronic Heart Disease ☐ Chronic Pulmonary Disease ☐

Chronic Liver Disease ☐ Chronic Kidney disease ☐

Occupation: _____

Vaccination status: Vaccinated within last three years: **Y / N / NK**

Pneumococcal Vacc **Y / N / NK**

Meningococcal Vacc: Polysaccharide **Y / N / NK;** Conjugate: **Y / N / NK**

Appendix 5

Recommendations for clinical management

(largely as developed for the DH in 2004).

- Clinical record keeping in critical illnesses requires improvement
  - *I recommend that all clinical records should contain more than 75% of essential information. Specific guidance should be given on documentation of disease severity which could be incorporated into a standard generic clerking proforma.*
  - *Patient record keeping should be monitored by the supervising consultant under the Trust clinical governance framework.*
  - *Particular focus should be put on recording these standards, as specified in the RCP Health Informatics Unit (HiU) evidence-based structured standards for record keeping:*
    - ***Standard 6*** - date, time, signature of the staff
    - ***Standard 7*** – to record the most senior staff at time of review
    - ***Standard 18*** - discharge summary information should be validated by a senior clinician.
    - ***Standard 30*** - doctors should participate in auditing medical records against evidence-based standards.
- **It is recommended that "*Laying the foundations for good medical practice*"** - a training programme for senior house officers (SHO) developed by the HiU and the Education Department of the Royal College of Physicians should be made mandatory for all first year SHOs (nowdays Foundation Training (FT)1 post)
- **First assessment, diagnosis and initial treatment is sub-optimal.**

- In patients with a suspected (by GP, triage nurse, ambulance, or other) diagnosis of bacterial meningitis or meningococcal septicaemia >90 should be reviewed by a staff grade doctor within 30 minutes of arrival.
- All patients with a final diagnosis should have been reviewed within 2 hours of arrival.
- A diagnosis of bacterial meningitis and meningococcal septicaemia should be suspected in >90% of patients with final diagnosis.
- Parenteral antibiotics should be given to >90% of patients with final diagnosis at first assessment and 100% of patients with suspected diagnosis.

❖ **Assessment and recording of severity of illness is suboptimal**

- >90% of severely ill patients (as defined in '*Standards and indicators*') should be reviewed by a staff grade doctor within 30 minutes of arrival.
- >90 of severely ill patients should be seen by a ICU team or consultant within 2hrs of admission.
- >90% of indicators of severity of illness should be recorded in the first assessment

❖ **Too few patients receive a timely assessment by the supervising consultant and specialist teams**

- >90% of all patients with final diagnosis should have been reviewed by a consultant within 6hrs of admission
- >90% of all patients with final diagnosis should have been reviewed by a ICU team within 12hrs of admission

This requires close collaboration between those working in acute medicine, infection specialties (microbiology and infectious diseases) and those working in critical care, with a greater emphasis on outreach multi-disciplinary consultation services.

❖ General recommendations for clinical management

➢ **Organisation of service**

- In line with recommendations of the RCP working party "*The interface between Acute General Medicine and Critical Care*" I recommend that consultants should participate on a dedicated on-call system where their sole responsibility is towards supporting emergency work, relating not only to the care of referrals to the medical intake from GPs and from the accident and emergency department (A&E), but also to the evaluation and management of acutely ill inpatients in all departments.
- I recommend that junior medical staff be increasingly involved in educational and training activities of the Intensive Care Unit services.
- I support the recommendation for introduction of Early Warning Scoring Systems appropriate to severely ill medical patients. Junior medical, nursing and allied health professionals (AHPs) must be trained in their use, both to enhance their recognition of the severely ill and to develop their ability to initiate management driven by appropriate protocols.
- I support the recommendation on the introduction of intensive care unit (ICU) outreach services, as specified in the publication *Comprehensive critical care: a review of adult critical services* (Department of Health, 2000).

➢ **Training**

- I recommend that training in the recognition and management of acutely ill patients should begin in medical school.
    - All undergraduates should receive training in advanced life support.

- Medical schools should consider developing training modules which focus on the knowledge and skills needed in the initial assessment of the severely ill, and which depart from organ system-based training in favour of an approach based on the recognition of the significance of physiological perturbations.

- Postgraduate deans should ensure that pre-registration house officers (PRHOs) develop these skills and are competent in assessing and managing severely ill patents.

- Postgraduate deans should locally adopt one of the nationally available generic training schemes (e.g. the Acute Life-threatening Events - Recognition and Treatment (ALERTTM) programme), designed to teach a systematic approach to the assessment and care of the severely ill.

- and make it a mandatory requirement for career progression beyond senior house officer (SHO) year 1.

- SpR training – I recommend that training in the management of the acutely ill patient with an infection should be formally included in both the curricula of general medicine and the specialties which are likely to be involved in the care of acutely ill medical patients.

❖ There is currently a major drive to replace existing paper records with electronic records by 2008 (this objective has now been changed "to have 60,000,000 patients with a centralized electronic medical record by 2010" [5]., but with no good standards of recording this would not be a useful exercise (Mann 2001). Structured record keeping are easier and quicker to search and therefore can improve decision-making and could enhance interpretation and therefore limit clinical errors, improving patient

[5] http://www.connectingforhealth.nhs.uk/newsroom

outcomes and reducing the costs of healthcare as well as improved data validity for secondary purposes (management, audit, etc)

❖ **Minimise differences between hospitals**

➢ Standardise the graduate and postgraduate training (see 2.2 Training)

➢ Standardise service provision across NHS acute trusts (see 2.1 Organisation of service)

➢ Standardise guidance on clinical management of these particular conditions (see 4.1 Recommended standards of management)

❖ **Facilitating the adherence to recommended standards of management**

➢ Developing standards of management

- The guidance published by the British Infection Society (BIS) is in line with the best evidence available and therefore should be reinforced by the appropriate bodies of the DH
- Produce (if not available) and distribute *Integrated care pathways* and *Clinical algorithms* (use the recently published from the BIS) based on the recommendations

➢ Dissemination and implementation of guidelines

- I recommend that a variety of implementation methods are considered and integrate them within any existing strategy for change
- Use education and training incorporated within career progression training (JHO, SHO and SpR) as well as continuous professional education (CPD) for more senior staff
- Use active learning in form of seminars within the local hospitals for targeted audience

- Use also other more active methods and techniques, such as clinical leadership, peer influence, facilitation, audit sanctions, marketing and reminders to facilitate take-up of recommendations
- Use feedback and reward for improving effective use of clinical guidelines

Appendix 6

Draft proposal for research funding

Bacterial meningitis in England and Wales: intervention to improve clinical management and examine its association with outcome

Background and introduction: Bacterial meningitis remains a grave disease amongst adults in E&W.

The progress in the control of meningococcal disease C due to the successful vaccination programme has been evidenced and is a great achievement – no deaths from confirmed Meningitis C were reported during 2007 in the vaccination age. However, the fatality from the other forms of CABM still remains high.

Two previous reviews of clinical management, amongst both children and adults, reviled serious deficiencies. In meantime there have been several interventions with aim to facilitate and improve management in line with guidelines, including the algorithm of emergency management; the publications of these reports in peer-reviewed journals; publication of handbook for management in children.

There isn't, however, evidence in support of change of behaviour on clinical management based on publication of guidelines or peer-reviewed publications. There is, though, some evidence from a systematic review that interactive interventions, such as seminars and the peer-trainer in the hospitals, does result in a better adherence to clinical guidelines.

Other recent structural interventions might also have a potential impact on the patients' care, such as: consultants' contract has generally resulted in a reduced working hours and the EWT directive also significantly reduced hours of work and training of junior doctors. For the clinical management of a relatively rare condition, such as meningitis, these could have serious implications.

The hospital review of adult management also suggest that some of the key clinical practices, including time to antibiotics, assessed by a consultant, time to diagnosis might have an impact on the outcome of cases. However as the study was not designed to test these associations it lacked power to prove a statistically significant association for most of them. The study of management of children and adolescents, also, suggested an increased uncertainty of the use of antibiotics in early treatment of meningitis; though it has been admitted that the potential unmeasured confounders could, at least in part, explain the negative association. It would, therefore be important to establish the association of clinical management with the outcome of the disease.

One of the major findings of this review was the substandard and varying level of record keeping. Given that this practice has repercussions in the actual management of cases, and that not only meningitis but any severe infection, I consider this needs further examination to assist the implementation of the management standards. Also, the RCP has this year recommended and produced a standard case-records form.

Experience from the original hospital review would be sufficient to account for the need for piloting the study and the instruments to be used. Also the data from my original study would be used as a comparison of potential changes in management of this disease over the time.

I would therefore like to propose a study that would aim to:

Examine the potential improvement in the management of CABM in adults in England and Wales against the standards published with the algorithm, including the medical record keeping;

Examine the association of the key clinical practices, including record keeping, with the outcome of the disease.

Study design: random intervention trial, retrospective review of medical case-notes.

3months intervention – 3 seminars, every month in 18 hospitals (evidence from systematic review as effective on guideline adherence); reminder 'tools': back of ID cards; stickers / magnets / plasticised hard sheets... with a key recommended indicators for clinical management of adult CABM and MS.

1 years review of cases; to start right after intervention. Study period June '10 – June '11.

Method – select and allocate hospitals randomly to intervention vs no-intervention. Retrospective review of case-records.

Intervention: peer intervention – selection /recruitment and training of senior staff to be peer trainers (at SpR level); a one day training – central; with support from Meningitis Research Foundation (producing standard training materials). The peers will then organise and deliver the 3 seminars in their own settings; with support, and quality assurance from the study's principal investigator and research fellow.

Timeline: July - Oct 2009: prepare; recruit research fellow, design study instruments

Start hospital recruitment / allocation Oct 2009

Selection / training of peer trainers Nov '09

Intervention Dec 2009 to February 2010

Data collection: start February 2011 to April 2012.

Study period of data to be collected:

i. baseline data1st November 2008 – 30th October 2009

ii. intervention data: February 2011 – January 2012.

Preliminary analysis and report 6 months from start.